The Journal
of the MICHIGAN State Medical Society
Volume 57, Number 5 May, 1958

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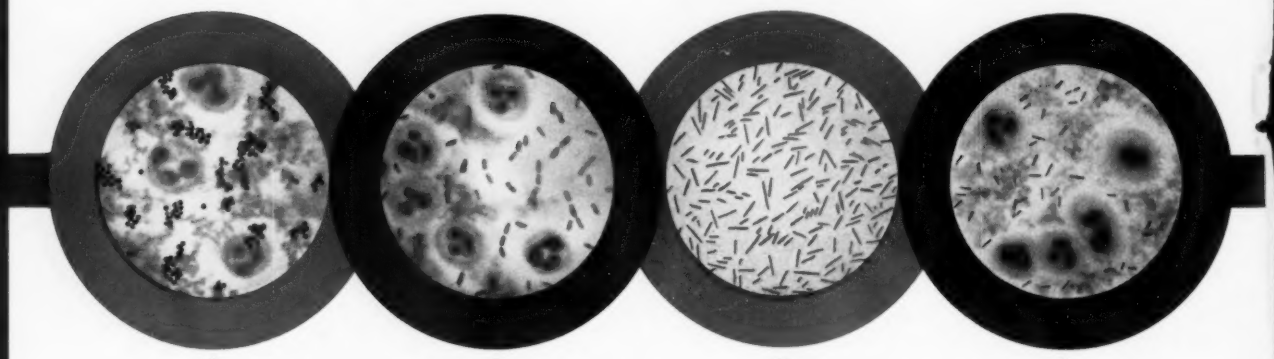

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REFERENCES: (1) Roy, T. E.; Collins, A. M.; Craig, G., & Duncan, I. B. R.: *Canad. M.A.J.* 77:844 (Nov. 1) 1957. (2) Schneierson, S. S. *J. Mount Sinai Hosp.* 25:52 (Jan.-Feb.) 1958. (3) Koch, R., & Donnell, G.: *California Med.* 87:313, 1957. (4) Waisbren, B. A., & Strelitzer, C. L.: A Five-Year Study of the Antibiotic Sensitivities and Cross Resistances of Staphylococci in a General Hospital, paper presented at Fifth Ann. Symp. on Antibiotics, Washington, D. C., Oct. 2-4, 1957. (5) Doniger, D. E., & Parenteau, Sr. C. M.: *J. Maine M. A.* 48:120, 1957. (6) Royer, A.: Changes in Resistance to Various Antibiotics of Staphylococci and Other Microbes, paper presented at Fifth Ann. Symp. on Antibiotics, Washington, D. C., Oct. 2-4, 1957. (7) Hasenclever, H. F.: *J. Iowa M. Soc.* 47:136, 1957. (8) Josephson, J. E., & Butler, R. W.: *Canad. M.A.J.* 77:567 (Sept. 15) 1957. (9) Rhoads, P. S.: *Postgrad. Med.* 21:563, 1957. (10) Holloway, W. J., & Scott, E. G.: *Delaware M. J.* 29:159, 1957.

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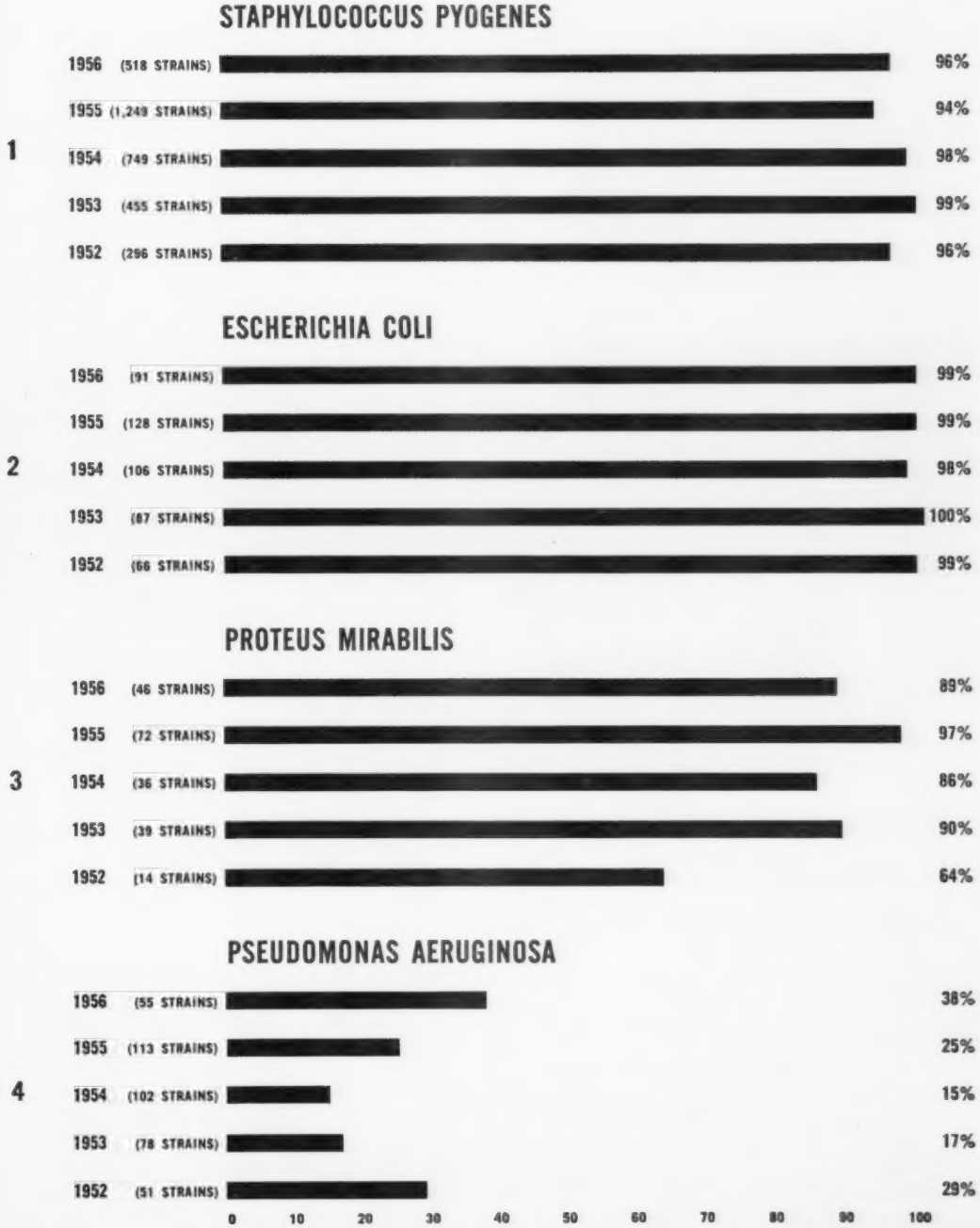
IN VITRO SENSITIVITY OF FOUR COMMON PATHOGENS TO CHLOROMYCETIN FROM 1952 TO 1956*



*Adapted from Roy and others.[1]

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VOLUME 57 MAY, 1958 NUMBER 5

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Heart Beats

HEART ASSOCIATION ELECTS OFFICERS

F. D. Dodrill, M.D., the Detroit heart surgeon who conceived and developed the first mechanical heart successfully used on human beings, took office as President of the Michigan Heart Association at the Association's annual board meeting held March 21, 1958, in Detroit. The meeting was held in conjunction with the Michigan Clinical Institute at the Sheraton-Cadillac Hotel.

F. D. Dodrill, M.D. (*left*), Detroit, who was elected President of the Michigan Heart Association, presents the Association's Certificate of Appreciation to M. S. Chambers, M.D., Flint, the retiring President. The presentation was made at the Association's annual Board meeting held in conjunction with the Michigan Clinical Institute, March 21.

Dr. Dodrill is a graduate of the Harvard Medical School and is a surgeon in the Thoracic Surgery Departments of Harper and Mt. Carmel Hospitals in Detroit. He is one of the original incorporators of the Michigan Heart Association and has served on its Board of Trustees continuously since its incorporation in February, 1949.

The original mechanical heart is now a permanent exhibit at the Smithsonian Institute in Washington, D. C. It was rated as one of the top ten scientific developments of 1952 by the National Association of Science Writers and it received the bronze Hektoen Award of the American Medical Association for original investigation in June, 1953. The General Motors Corporation Research Laboratories undertook the engineering phase of the development of the mechanical heart as a public service. Dr. Dodrill is the author of numerous manuscripts on the development of the heart-lung bypass operation.

At the same meeting, Donald S. Smith, M.D., a Pontiac internist, was named President-elect. Dr. Smith has served as chairman of the Association's Research Committee for the past three years. Mr. Frank N. Isbey, Detroit, was elected chairman of the MHA Board of Trustees. Mr. Isbey was one of the original incorporators of the Michigan Heart Association and has served as chairman of the Finance Committee since its incorporation in 1949.

Other officers named were: Sidney E. Chapin, M.D., Dearborn, Secretary and Mr. Alfred T. Wilson, Detroit, Treasurer. The following persons were elected as Vice Presidents: Muir Clapper, M.D., and Mrs. Ruth McEvoy of Detroit; F. D. Johnston, M.D., of Ann Arbor and Milton Shaw, M.D., of Lansing.

Dr. Dodrill made the following standing committee appointments at the meeting:

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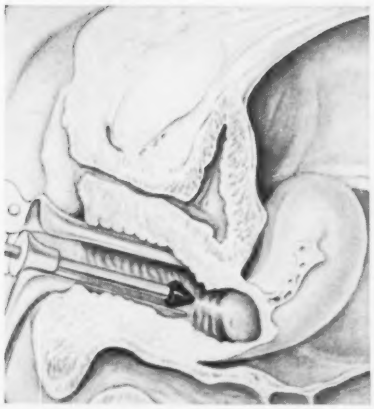
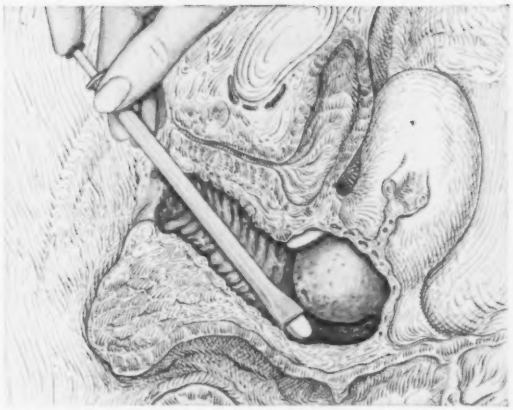
(Continued on Page 777)

COMPREHENSIVE VAGINITIS REGIMEN



Powder Insufflation



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*Williamson, P.: Trichomonad Infestation, M. Times *84*:929 (Sept.) 1956.

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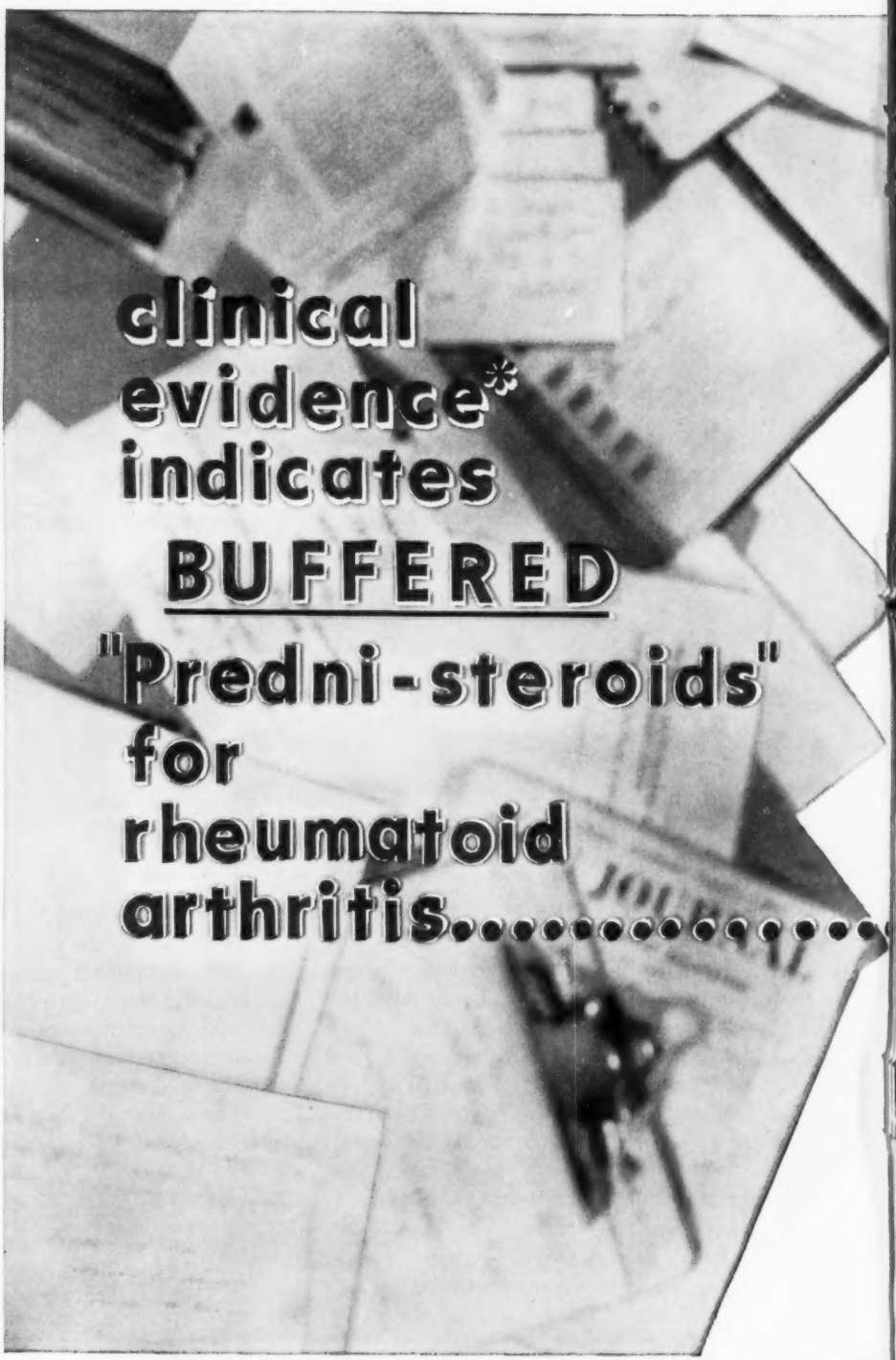
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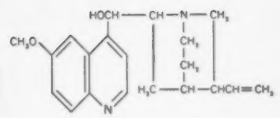

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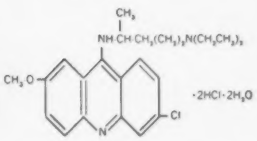

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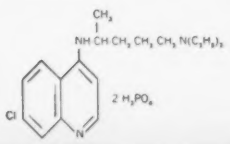

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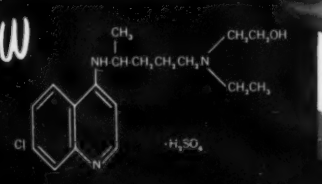

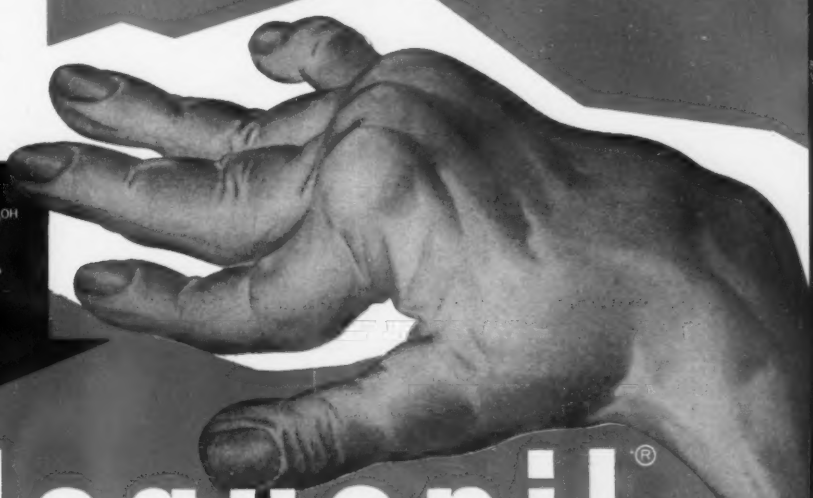

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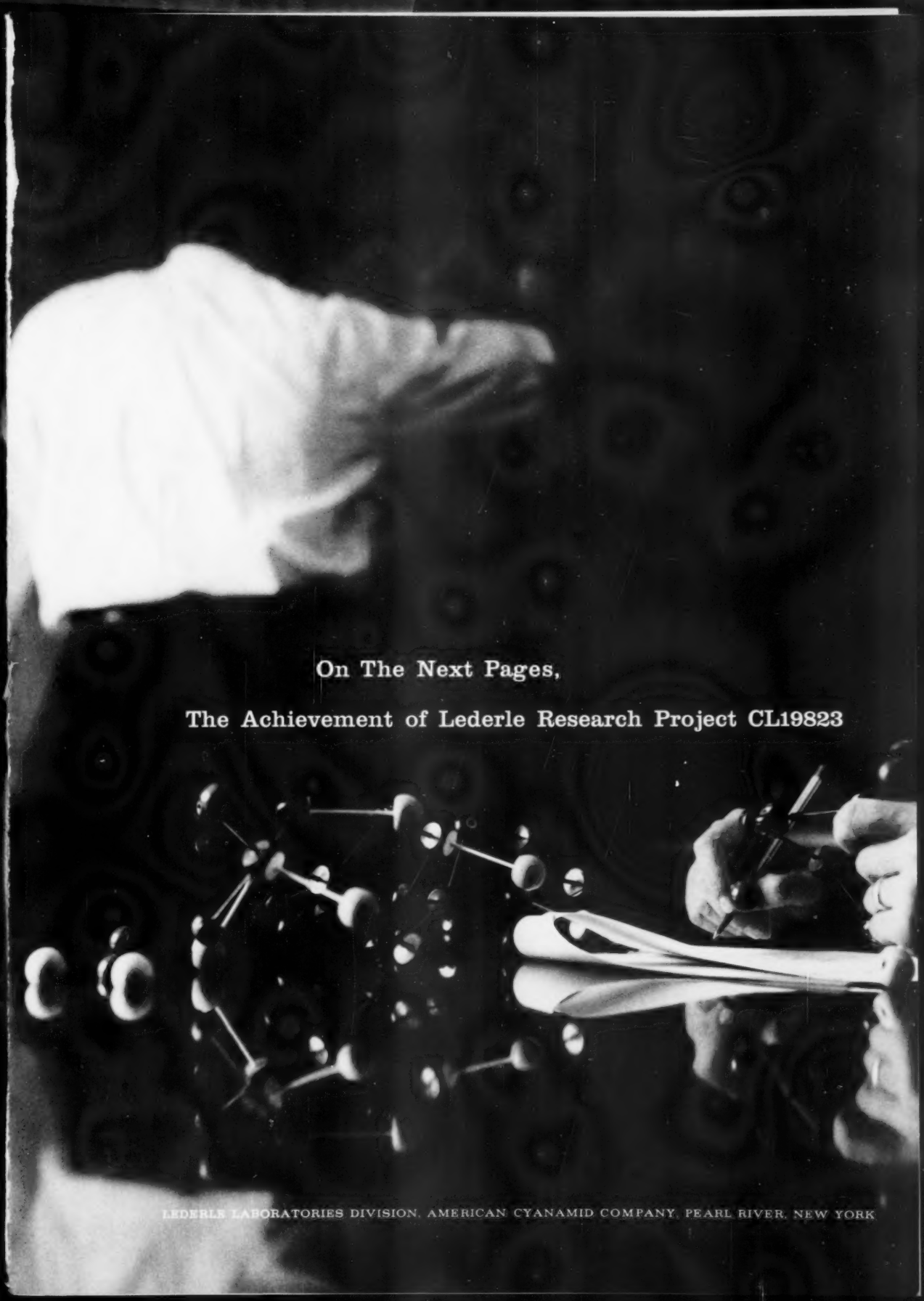
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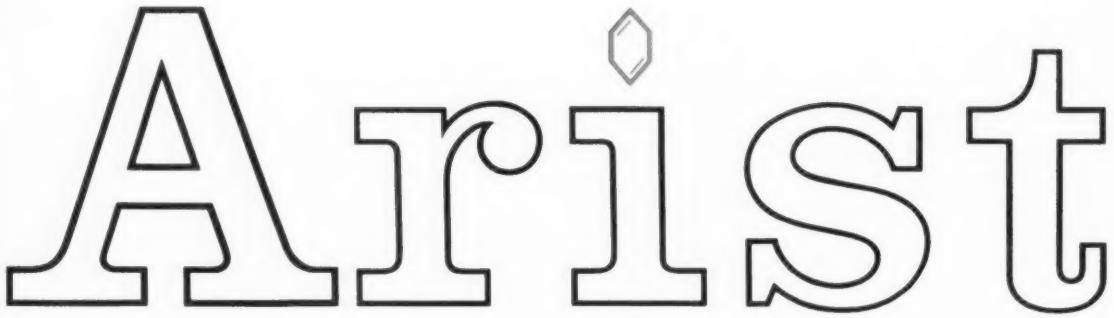

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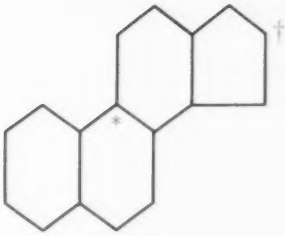

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Biological Effects of Aristocort

with particular emphasis on:

Kidney function

Animal studies on ARISTOCORT[1] have not demonstrated any interference with creatinine or urea clearance. Autopsy surveys of organs of animals on prolonged study of this medication have shown no renal damage.

Sodium and water

ARISTOCORT produced an increase of 230 per cent of water diuresis and 145 per cent sodium excretion when compared to control animals.[1] Metabolic balance studies in man revealed an average negative sodium balance of 0.8 Gm. per day throughout a 12-day period on a dosage of 30 mg. per day.[2] Additional balance studies showed actual sodium loss when ARISTOCORT was given in doses of 12 mg. daily.[3] Other investigators observed significant losses of sodium and water during balance studies and that those patients with edema from some older corticosteroids lost it when transferred to ARISTOCORT.[4,5] In two studies of various rheumatic disorders (194 cases) on prolonged treatment, sodium and water retention was not observed in a single case.[6,7]

Potassium and chlorides

There was no active excretion of potassium or chloride ions in animals given maintenance doses of ARISTOCORT 25 times that found to be clinically effective.[1] Potassium balance studies in humans[2,3] revealed that negative balance did not occur even with doses somewhat higher than those employed for prolonged therapy in rheumatoid arthritis. Hypokalemia, hyperkalemia or hypochloremia did not occur, when tested, in 194 patients with rheumatoid arthritis treated for up to ten and one-half months.[6,7]

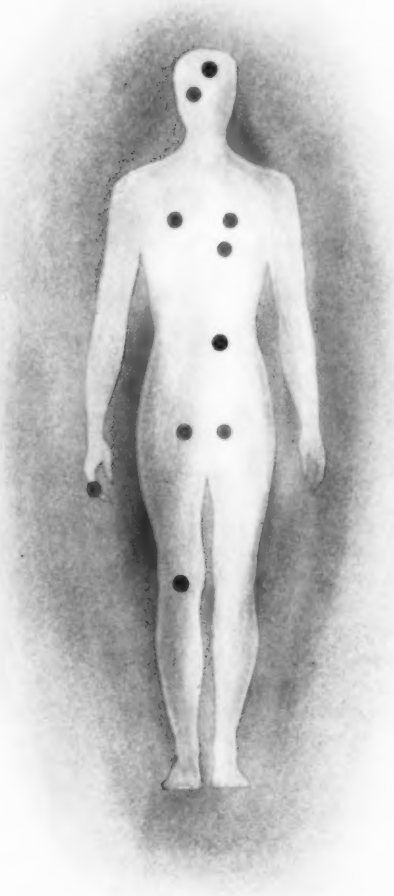
Calcium and phosphorus

Phosphate excretion in animals[1] was not changed from normal even with amounts 25 times greater (by body weight) than those known to be clinically effective. Human metabolic balance studies[3] demonstrated that no change in calcium excretion occurred on dosages usually employed clinically when the compound is administered for its anti-inflammatory effect. Even at a dosage level twice this, slight negative balance appeared only during a short period.

Protein and nitrogen balance

Positive nitrogen balance was maintained during a human metabolic study on maintenance dosage of 12 mg. per day.[3] At dosages two to three times normal levels, positive balance was maintained except for occasional short periods in metabolic studies of several weeks' duration.[2,3]

There was always a tendency for normalization of the A/G ratio and elevation of blood albumin when ARISTOCORT was used in treating the nephrotic syndrome.[8]



Liver glycogen deposition and inflammatory processes

An intimate correlation exists between the ability of a corticosteroid to cause deposition of glycogen in the liver and its capacity to ameliorate inflammatory processes.

In animal liver glycogen studies, relative potencies of ARISTOCORT over cortisone of up to 40 to 1 have been observed. Compared to ARISTOCORT, five to 12 times the amount of prednisone is required to produce varying but equal amounts of glycogen deposition in the liver.[1]

Most patients show normal fasting blood sugars on ARISTOCORT. Diabetic patients on ARISTOCORT may require increased insulin dosage, and occasional latent diabetics may develop the overt disease.

Anti-inflammatory potency of ARISTOCORT was determined by both the asbestos pellet[1] and cottonball[9] tests. It was found to be nine to 10 times more effective than hydrocortisone in this respect.

Gastric acidity and pepsin

The precise mode of ulcerogenesis during treatment with corticosteroids is not known. There is much experimental evidence for believing this may be related to the tendency of these agents to increase gastric pepsin and acidity—and this cannot be abolished by vagotomy, anticholinergic drugs or gastric antral resection.[10] Clinical studies[11] of patients on ARISTOCORT revealed that uropepsin excretion is not elevated. Further, their basal acidity and gastric response to histamine stimulation were within normal limits.

Central nervous system

The tendency of corticosteroids to produce euphoria, nervousness, mental instability, occasional convulsions and psychosis is well known.[12] The mechanism underlying these disturbances is not well understood.

ARISTOCORT, on the contrary, does not produce a false sense of well being, insomnia or tension except in rare instances. In the treatment of 824 patients, for up to one year, not a single case of psychosis has been produced. In general, it appears to maintain psychic equilibrium without producing cerebral stimulation or depression.

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Lederle

The Promise of Aristocort in Reduction of Side Effects

It is axiomatic to affirm that the undesirable collateral hormone effects of corticosteroids increase in frequency and severity the higher the dosage and the longer used.

It has also become well recognized that the most serious of the major side effects from long-term corticosteroid treatment are peptic ulcers, osteoporosis with fracture, drug psychosis and euphoria, and sodium and water retention leading often to general tissue edema and hypertension.

It is significant that of the close to 400 patients on the lower dosage schedules found effective in bronchial asthma and dermatologic conditions, only 1 case of peptic ulceration has developed. No other of the above side effects have been observed even though ARISTOCORT was administered continuously to them for periods as long as one year.

The treatment of rheumatoid arthritis with steroids appears to result in the highest incidence of side effects. For this reason, the side effects associated with ARISTOCORT therapy in 292 patients with rheumatoid arthritis are reported below.

Peptic Ulcer

The occurrence of peptic ulcer in 292 patients with rheumatoid arthritis treated continuously for up to one year with ARISTOCORT is approximately 1 per cent (2 of the 3 occurred in patients transferred from prednisone). In the remaining 532 cases recently analyzed, only one ulcer has been discovered in a patient who apparently had no ulcer when he was changed from another steroid.

Osteoporosis and Compression Fractures

The occurrence of osteoporosis with compression fracture in 292 patients with rheumatoid arthritis treated continuously for up to one year with ARISTOCORT is 0.33 per cent (1 case[1]). Although these results are encouraging, determination of the true incidence of osteoporosis will have to await the passage of more time.

Euphoria and Psychosis

The euphoria so commonly produced by all previous corticosteroids has seemed a most desirable attribute to patients. In penalty, however, they have often later to pay for this by mental disturbances, varying from mild and transitory to severe depression and psychosis,[2] and toxic syndromes producing even convulsions and death.[3]

Since the onset of these complications is not directly related to duration of steroid administration,[4] the fact that not one case of psychosis occurred in 824 patients treated with ARISTOCORT, is most encouraging.

Sodium Retention—Hypertension-Potassium Depletion

When 17 patients were changed from prednisone to ARISTOCORT, 11 rapidly lost weight although only one had had visible edema.[5] Sodium and water retention, hypokalemia or hyperkalemia and steroid hypertension did not appear in 194 rheumatoid arthritis patients treated with ARISTOCORT.[1,6]

The interrelation between blood and body sodium, and steroid hypertension has long been generally appreciated.[7,8] Except in rare instances, or when unusually high doses are used (e.g., leukemia), the problem of edema and hypertension caused by sodium and water retention, has been eliminated with ARISTOCORT.

Minor Side Effects

Collateral hormonal effects of less serious consequence occurred with approximately the same frequency as with the older corticosteroids.[1] These include erythema, easy bruising, acne, hypertrichosis, hot flashes and vertigo. Several investigators have reported symptoms not previously described as occurring with corticosteroid therapy, e.g., headaches, lightheadedness, tiredness, sleepiness and occasional weakness.

Moon facies and buffalo humping have been seen in some patients on ARISTOCORT. However, ARISTOCORT therapy, in many instances, resulted in diminution of "Cushingoid" signs induced by prior therapy. Where this occurs, it may be related to reduced dosage on which patients can be maintained.

Reduction of dosage by one-third to one-half

In a double-blind study of comparative dosage in patients with rheumatoid arthritis,[9] 70 per cent of the cases were as well controlled on a dose of ARISTOCORT one-half that of prednisone. A general recommendation can be made that ARISTOCORT be used in doses two-thirds that of prednisone or prednisolone in the treatment of rheumatoid arthritis. There are individual variations, however, and each patient should be carefully titrated to produce the desired amount of disease suppression.

Comparative studies, of patients changed from prednisone, indicate reduced dosage of ARISTOCORT in bronchial asthma and allergic rhinitis (33 per cent),[5] and in inflammatory and allergic skin diseases (33-50 per cent).[10,11]

General Precautions and Contraindications

Administration of ARISTOCORT has resulted in lower incidence of major serious side effects, and in fewer of the troublesome minor side effects known to occur with all previously available corticosteroids. However, since it is a highly potent glucocorticoid, with profound metabolic effects, all traditional contraindications to corticosteroid therapy should be observed.

No precautions are necessary in regard to dietary restriction of sodium or supplementation with potassium.

Since ARISTOCORT has less of the traditional side effects, the appearance of sodium and water retention, potassium depletion, or steroid hypertension cannot be used as signs of overdosage. As a rule patients will lose some weight during the first few days of treatment as a result of urinary output, but then the weight levels off.

Patients do not develop the abnormally voracious appetite common to previous corticosteroid administration. In fact, some patients experienced anorexia, and it is advisable to inform patients of this and to recommend they maintain a normal intake of food, with emphasis on liberal protein intake.

While precipitation of diabetes, peptic ulcer, osteoporosis, and psychosis can be expected to appear rarely from ARISTOCORT, they must be searched for periodically in patients on long-term steroid therapy.

Traditional precautions should be observed in gradually discontinuing therapy, in meeting the increased stress of operation, injury and shock, and in the development of intercurrent infection.

There is one overriding principle to be observed in the treatment of any disease with ARISTOCORT. *The amount of the drug used should be carefully titrated to find the smallest possible dose which will suppress symptoms.*

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The Promise of Aristocort in Rheumatoid Arthritis

◇ ARISTOCORT *therapy has been intensely and extensively studied for periods up to one year on 292 patients with rheumatoid arthritis.*

Significant is the fact that most patients were *severe* arthritics, transferred to ARISTOCORT from other corticosteroids because satisfactory remission had not been attained, or because the seriousness of collateral hormonal effects had made discontinuance desirable.

Results of treatment

Freyberg and associates[1] treated 89 patients with rheumatoid arthritis (A. R. A. Class II or III and Stage II or III). Of these, 51 were on ARISTOCORT therapy from three to over 10 months. In all but a few patients, satisfactory suppression of rheumatoid activity was obtained with 10 mg. per day. Thirteen were controlled on 6 mg. or less a day, and for periods to 180 days. The investigators reported therapeutic effect in most cases to be A. R. A. Grade II (impressive) and that marked reduction in sedimentation rates occurred.

Another interesting observation in this study: Of the 89 patients treated, 12 had active ulcers, developed from prior steroid therapy. *In six patients, the ulcers healed while on doses of* ARISTOCORT *sufficient to control arthritic symptoms.*

Hartung[2] treated 67 cases of rheumatoid arthritis for up to 10 months. He found the optimum maintenance dose to be 11 mg. per day. Nineteen of these patients were treated for six to 10 months with an "excellent" therapeutic response.

Dosage and course of therapy

The initial dosage range recommended is 14 to 20 mg. per day—depending on the severity and acuteness of signs and symptoms. Dosage is divided into four parts and given with meals and at bedtime. Anti-rheumatic effect may be evident as early as eight hours, and full response often obtained within 24 hours. This dosage schedule should be continued for two or three days, or until all acute manifestations of the disease have subsided, whichever is later.

The maintenance level is arrived at by reduction of the total daily dosage in decrements of 2 mg. every three days. The range of maintenance therapy has been found to be from 2 mg. to 15 mg. per day—with only a very occasional patient requiring as much as 20 mg. per day. Patients requiring more than this should not be long continued on steroid therapy.

The aim of corticosteroid therapy in rheumatoid arthritis is to suppress the disease only to the stage which will enable the patient to carry out the required activities of normal living or to obtain reasonable comfort. The maintenance dose of ARISTOCORT to achieve this end is arrived at while making full use of all other established methods of controlling the disease.

ARISTOCORT is available in 2 mg. scored tablets (pink); 4 mg. scored tablets (white). Bottles of 30.

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Lederle

The Promise of Aristocort in Respiratory Allergies

About 200 patients with respiratory allergies have been treated with ARISTOCORT *for continuous periods up to eight months.*

Results of treatment

Sherwood and Cooke[1, 2] gave ARISTOCORT to 42 patients with bronchial asthma and allergic rhinitis. Average dose needed to control the asthmatic group was approximately 6 mg. per day (range, 2 to 14 mg.). Results, which were called "good to excellent" in all but four, were achieved on one-third less than similarly effective doses of prednisone or prednisolone.

The investigators noted other major improvements in ARISTOCORT therapy over the older steroids. There was no increase in blood pressure in any patient: *on the contrary, in 12 patients, there was reduction of pressure when they were transferred to* ARISTOCORT. One patient had required auxiliary antihypertensive drug therapy; over a nine-week period on ARISTOCORT, the pressure gradually fell from 206/100 to 136/79. In another case, the pressure slowly dropped from 205/105 to 154/86.

The number of cases in which these investigators tried ARISTOCORT in allergic rhinitis was not large enough to provide significant averages. However, the range of effective therapy was from 2 to 6 mg. per day. These strikingly low daily doses resulted in control of all signs and symptoms.

Schwartz[3] treated 30 patients with chronic, intractable bronchial asthma. At an average daily dose of 7 mg., he reported "good to excellent" results in all but one. Spies,[4] Barach[5] and Segal,[6] reported similar results at average daily maintenance doses of 4 to 10 mg. of ARISTOCORT.

Dosage and course of therapy

The initial dosage range recommended is 8 to 14 mg. of ARISTOCORT daily. Although a rare, very severe case may require more than this on the first day of therapy, these dosages will usually result in prompt alleviation of dyspnea, wheezing and cyanosis. Patients are soon able to carry out a normal span of daily activity.

The maintenance level is arrived at by reduction of the total daily dose every three days in decrements of 2 mg.; in the over-all series, the average daily dose for bronchial asthma is approximately 8 to 10 mg. and for allergic rhinitis, 2 to 6 mg. per day. All total daily doses should be divided into four parts and given with meals and at bedtime. As in every condition where corticosteroids are employed, each patient's treatment should be individualized and the maintenance arrived at by careful titration against signs and symptoms of disease.

Patients with chronic bronchial asthma may require steroid therapy for several months. And since asthma may be associated with cardiac disease, especially in the older age groups, ARISTOCORT is particularly useful because of its ability to cause excretion of sodium and water.

ARISTOCORT is available in 2 mg. scored tablets (pink); 4 mg. scored tablets (white). Bottles of 30.

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Lederle

The Promise of Aristocort

in Nephrotic Syndrome

◯ *Fourteen patients with the nephrotic syndrome have been treated with* ARISTOCORT *for continuous periods of up to six weeks.*

Results of treatment

Hellman and associates[1,2] noted that ARISTOCORT, because of its favorable electrolyte effects, may well be the most desirable steroid to date in treatment of the nephrotic syndrome. However, thus far its use has been reported in only 14 children, of whom 8 had a complete diuresis and disappearance of all abnormal chemical findings. Four of the patients had diuresis, but continued to show some abnormal chemical findings, while two patients with signs of chronic renal disease failed to respond.

Dosage and course of therapy

In order to produce maximal response, 20 mg. should be given daily until diuresis occurs. The dose should then be decreased gradually and maintained around 10 mg. a day. After the patient has been in remission for some time, it may be advisable to diminish the dose gradually and discontinue ARISTOCORT.

in Pulmonary Emphysema and Fibrosis

◯ *Eleven patients with pulmonary emphysema and/or fibrosis were treated with* ARISTOCORT *for continuous periods of over two months.*

Results of treatment

Only small series of cases observed by Barach,[3] Segal,[4] and Cooke,[5] are available. Barach treated patients who were not adequately controlled by prednisone, with the same dose of ARISTOCORT with significant improvement.

Dosage and course of therapy

The initial suppressive dose range recommended is 10-14 mg. daily. Frequently, there is a prompt decrease in cyanosis and dyspnea, with increase in vital capacity.

The average maintenance dose level was 8 mg. a day. If it is desired to maintain a patient on continuous therapy for some months, dosages as low as 2 mg. a day have been successful. All decreases in dosage should be gradual and at a rate of 2 mg. decrements in total daily amount, every two to four days. The daily dosage is divided into four parts and given with meals and at bedtime.

in Neoplastic Diseases

Forty-four children and adults have been given ARISTOCORT *for palliative treatment of acute leukemia, chronic lymphatic leukemia, lymphosarcoma, lympholeukosarcoma and Hodgkin's disease.*

Results of treatment

Farber[6] has treated 22 children with acute leukemia for an average of three weeks. Of the 17 observed long enough to judge the efficacy of the medication, he rated five as excellent, three as good, two as fair and seven as poor responses.

Hellman and associates[7] gave ARISTOCORT to a group of patients with the various lymphomas in doses of 40 to 50 mg. a day—occasionally up to 100 milligrams. Treatment was continued in some cases for 17 weeks. Response was classified as good for the palliative purposes for which the drug was given.

Dosage and course of therapy

Massive initial suppressive doses of 40 to 50 mg. per day in children (1 mg./kg./day) and up to 100 mg. a day in adults have been administered.

Responses to any specific dosage in these conditions vary so widely that only a general dosage range can be indicated. Treatment must be individualized; rate of reduction in dosage and determination of maintenance levels cannot be categorized.

Miscellaneous

Patients with various other diseases have been treated by several clinical investigators. These include patients with osteoarthritis, acute bursitis, rheumatic fever, spondylitis, other "collagen-vascular" diseases (dermatomyositis, etc.), thrombocytopenic purpura, chronic eosinophilia, hemolytic anemia, diuretic-resistant congestive heart failures, and adrenogenital syndrome.

There have not been sufficient patients in any of the above categories to permit definitive treatment schedules to be finally established for ARISTOCORT. Additional studies are now in progress and physicians desiring information on any of these diseases are requested to write to Lederle Laboratories, Pearl River, New York for available data.

ARISTOCORT is available in 2 mg. scored tablets (pink); 4 mg. scored tablets (white). Bottles of 30.

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The Promise of Aristocort

in Inflammatory and Allergic Skin Diseases

◇ *Over 200 patients with allergic and inflammatory skin diseases (including psoriasis, atopic dermatitis, exfoliative dermatitis, pemphigus, dermatitis herpetiformis, eczematoid dermatitis, contact dermatitis and angioneurotic edema) have been treated continuously with* ARISTOCORT *for periods of up to eight months.*

Results of treatment

Rein and associates[1] treated 26 patients with severe dermatitis. Twenty-four had been on prednisone when changed to ARISTOCORT. While some had found satisfactory symptomatic relief, others had also developed side effects—moon face, buffalo hump, increased appetite with excessive weight increases and gastro-intestinal disturbances.

These investigators determined the equivalent dosage of ARISTOCORT to be approximately two-thirds that required to control symptoms on the previous corticosteroid. Thirteen of the 26, who had developed moon face, noted either an actual decrease or no further increase when transferred to ARISTOCORT. In addition: *Voracious appetites disappeared, with loss of weight in 11 patients; there was no elevation in blood pressure, and no necessity to restrict sodium or administer supplemental potassium.* Sherwood and Cooke,[2] and Shelley and Pillsbury[3] obtained similar results in allied disorders.

Hollander[4] first observed that ARISTOCORT appears to have striking affinity for the skin and great activity in controlling such diseases as psoriasis, for which other corticosteroids have been indifferently effective. Shelley and Pillsbury,[3] in 50 cases of acute extending psoriasis found that over 60 per cent were markedly improved.

Dosage and course of therapy

The recommended initial suppressive dose range is 14 to 20 mg. per day. In very severe cases, temporary dosages up to 32 mg. a day have been successfully employed. Once lesions are suppressed, gradually reduce dose to the maintenance level—which may be as low as 2 mg. per day.

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in Disseminated Lupus Erythematosus

◇ *Forty patients with disseminated lupus erythematosus were treated with* ARISTOCORT *for continuous periods of up to nine months.*

Results of treatment

Patients have responded very promisingly to therapy. Dubois[1] has had the largest single experience (28 cases) with ARISTOCORT in the treatment of this disease. He reported 25 of the 28 responded favorably.

Freyberg,[2] Hartung,[3] Hollander,[4] Spies,[5] and Segal,[6] each in smaller series of cases, reported similarly good therapeutic responses.

Dosage and course of therapy

The initial suppressive dose recommended is 20-30 mg. daily. Once the desired effect is achieved, the dose should be reduced gradually to maintenance levels (3 to 18 mg. per day).

In severely ill patients large doses may be required for several days in order to preserve life. Even on these large doses, edema and sodium retention have not occurred.

ARISTOCORT is available in 2 mg. scored tablets (pink); 4 mg. scored tablets (white). Bottles of 30.

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Editorial Comment

THE POLIO MIRACLE IS FIVE YEARS OLD

Time passes so quickly that perhaps only the medical profession is aware that it was just five years ago today—on March 26, 1953—that a modern miracle was announced.

It was on that day that Dr. Jonas E. Salk of the University of Pittsburgh announced that he had developed a new vaccine capable of immunizing people against polio.

Results since that day have been spectacular. More than 64 million persons in this country alone received one or more injections against polio in those five years. The U. S. Public Health Service reports that the incidence of paralytic polio has been reduced 84 per cent in the last two years. In the decade preceding the use of the vaccine, 30,000 to 40,000 cases of polio were recorded in this country every year. In 1952, the year before the vaccine was announced, 57,740 cases were recorded. In 1957, there were only 5,946 cases. Of these, 36 per cent were paralytic, 48 per cent non-paralytic, and 16 per cent unspecified.

Inasmuch as the polio "disease year" begins on April 1, the challenge continues to present itself, and efforts should be made particularly to inoculate children under five—although less than one-third of all persons under forty have received the maximum protection available to them. But five years after the miracle, it is satisfying to be able to report tremendous progress. Once again the public must co-operate fully with its medical men if the best possible results are to be achieved.—*Battle Creek Enquirer-News*, March 26, 1958.

GOOD HEALTH FROM APPLES?

It's a wonder the medical profession hasn't thrown a picket line around Michigan State University on the grounds that the school is unfair to physicians.

We're just spoofing, of course, but consider, for a moment, the experiment now being conducted by the MSU horticulture department in an effort to prove whether an apple a day really does "keep the doctor away."

The test calls for 500 students to consume a total of 7,000 apples every week for four years. Now then, what will it mean if results prove the truth of the old adage? It will mean, by simple multiplication, that 1,456,000 doctors will be kept away—thrown out of work! Is that fair?

Well, the experiment does promise to be an interesting one, and may well prove something health-wise. If not, it certainly won't do the apple crop any harm.—*Battle Creek Enquirer-News*, March 27, 1958.

A FABLE?

One warm afternoon in June the eighty-fourth amendment to the Social Security Act was passed in a welter of last-minute pre-vacation legislation. Only a few naïve freshmen and a brace of die-hards in Congress had bothered to even review these amendments in recent years. To oppose them meant a seat on the sidelines after November. 40% of all taxpyayers were now over the magic age of fifty-six and thus vitally interested in their passage. A few strokes of the pen and the Disability Insurance "Trust" Fund had become The Health Insurance "Trust" Fund. The President inspired deeply and signed. The death of the private practice of medicine was that simple.

A spokesman for the American Medical Association was quoted as "giving this ogre six months to live." Without doctors, "medical care for all" seemed a fatuous promise.

Somehow doctors appeared. Only a few, of course, from the fringe. These were promptly expelled by the various chapters and the fraternity held firm. Or nearly firm. One could not refuse the call of an old patient in critical condition. Mild censures followed, but generally this practice seemed only humane, and more and more "emergencies" were condoned. As the economic fat pad began to melt new frictions appeared. Ugly rumors were heard, denied, repeated and, alas, finally proven.

Virtuous martyrdom gave way to probing self-examination as the official posture of the organization faltered. The fee schedule, it was admitted, was more than generous. The rugged individualist had perished, in fact, two decades ago. Also there were the new security and retirement features. A man could get along, but he surely owed something to his family. Only the patient, after all, was suffering as a result of this political stalemate. The steadfast idealist in the mirror curiously took on the look of a stubborn fool.

In several pressure areas county societies voted secession rather than the continuation of practice under the existing double standard which had evolved. This was viewed as a step requiring great moral courage by unions, mass communication media, and surprisingly, by a significant body of the profession. And then creaking platform collapsed.

Later, of course, the fee schedule was revised—and re-revised. The descent of the qualifying age was matched only by the rise in taxes. Thus was Utopia born.—*Calhoun County Bulletin*, April, 1958.

Women, traditionally the weaker sex, are rapidly becoming much hardier than men in one major health area, according to a new publication, *Patterns of Disease*, prepared by Parke, Davis & Company for the medical profession.

It shows that while in 1915 the two sexes faced the same death risk from heart disease, the death risk for women is now one half of that for men.

PR REPORT

INGHAM COUNTY SOCIETY EXHIBITS AT HOME-ORAMA

The Ingham County Medical Society participated in the 1958 Lansing Home-arama, held for five days in the new Civic Center exhibition hall, beginning, March 26. Sponsored by the Lansing Home Builders Association and the Junior Chamber of Commerce, this free show attracted an attendance of 49,000 people.

Featured in the medical society's display were the MSMS emergency medical card and family health record which were distributed to the public. Several hundred visitors also had their blood drawn for free typing, Rh and blood sugar determinations. The latter rapid screening test was done on the spot with people watching the Clinitron in action. More than 1800 visitors also took advantage of the mobile chest x-ray service.

With doctors manning the booth as hosts, other personnel included members of the medical auxiliary, Ingham County Medical Assistants Society, and Michigan State Health Department Laboratory. Co-operating also in the project were the Ingham Chest Hospital and Mr. John K. Pardee, Michigan State Medical Society Field Secretary.

The exhibit was well received and was publicized by the Home-arama as a public service of the Ingham County Medical Society.

ORIGINS OF SELF REGULATION IN MEDICINE: PART IV

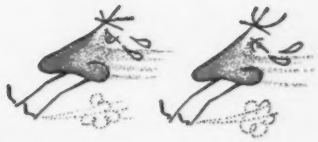
By Gaylord S. Bates, M.D.

The plan instituted by the Norman King Roger at Salerno, reinforced by the regulations of Frederick II of Hohenstaufen now became the practice in other European universities. The student had to pass an examination to become a bachelor and another to become a licentiate which conferred the right to practice. The license was usually conferred by the university chancellor who was often a cleric representing the pope. A further examination conferred the title of doctor which carried the privilege and duty of teaching for a time. Whoever practiced without a license was excommunicated and often punished by municipal authorities. The license gave the privilege of practice in all Christian countries. When a physician moved from one city to another he had to obtain permission from the municipal authorities to settle there, as did every person who

(Continued on Page 662)

This is the fourth installment of a paper presented before the Detroit Academy of Medicine at the Dearborn Inn, November 12, 1957.

running noses . . .



caused by pollen allergies

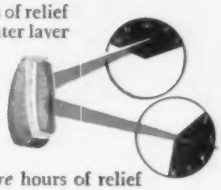
TRIAMINIC stops rhinorrhea, congestion and other distressing symptoms of summer allergies, including hay fever. Running nose, watery eyes and sneezing are best relieved by antihistamine *plus* decongestant action – systemically – with TRIAMINIC.

This new approach frequently succeeds where less complete therapy has failed. It is not enough merely to use histamine antagonists; ideally, therapy must be aimed also at the congestion of the nasal mucosa. Triaminic provides such effective combined therapy in a single timed-release tablet.

TRIAMINIC brings relief in minutes—lasts for hours. Running noses stop, congested noses open—and stay open for 6 to 8 hours.

Triaminic provides around-the-clock freedom from allergic congestion with just one tablet t.i.d. because of the special timed-release design.

first—3 to 4 hours of relief from the outer layer



then—3 to 4 *more* hours of relief from the inner core

Dosage: One tablet in the morning, mid-afternoon and at bedtime. In postnasal drip, one tablet at bedtime is usually sufficient.

Each timed-release TRIAMINIC Tablet contains:

Phenylpropanolamine HCl	50 mg.
Pheniramine maleate	25 mg.
Pyrilamine maleate	25 mg.

TRIAMINIC FOR THE PEDIATRIC PATIENT

TRIAMINIC Juvelets*, providing easy-to-swallow half-dosages for the 6- to 12-year-old child, with the timed-release construction for prolonged relief.

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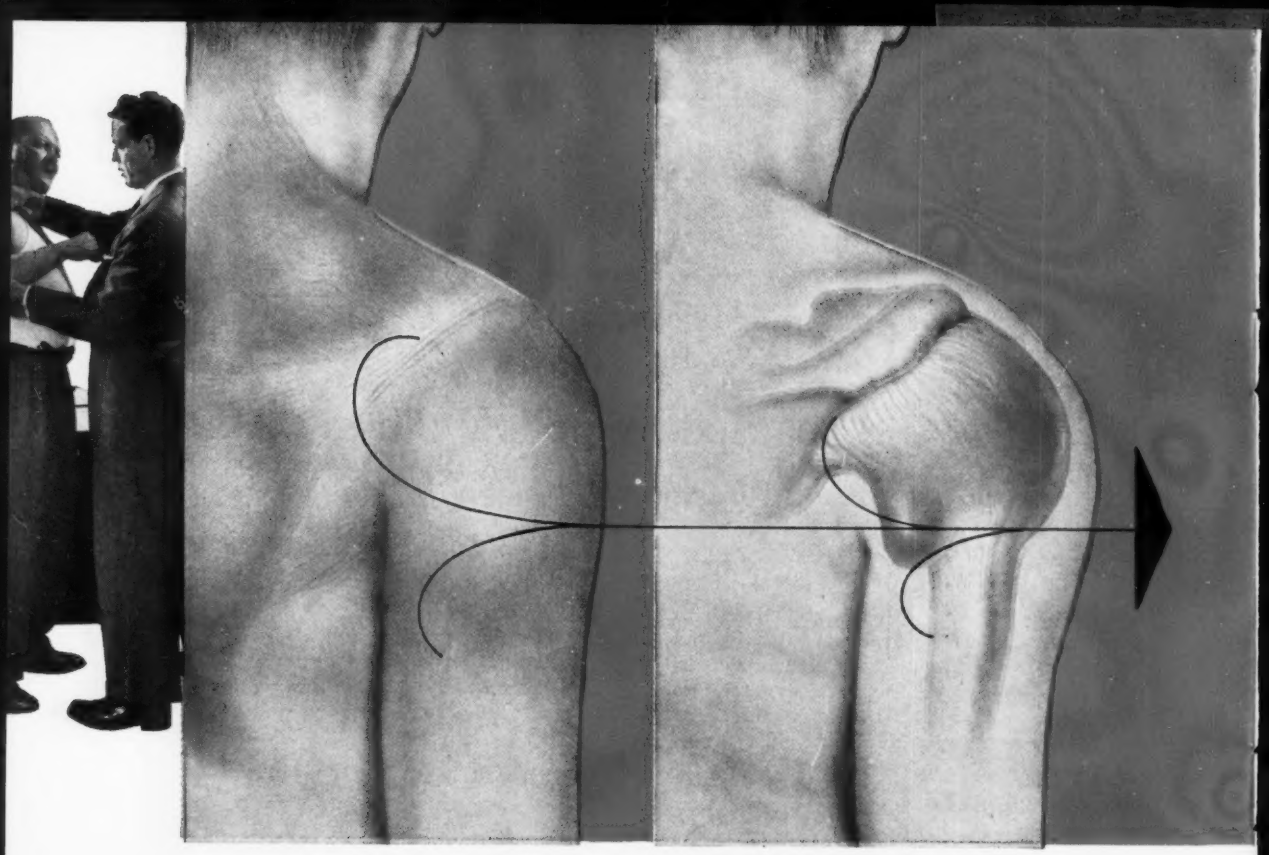
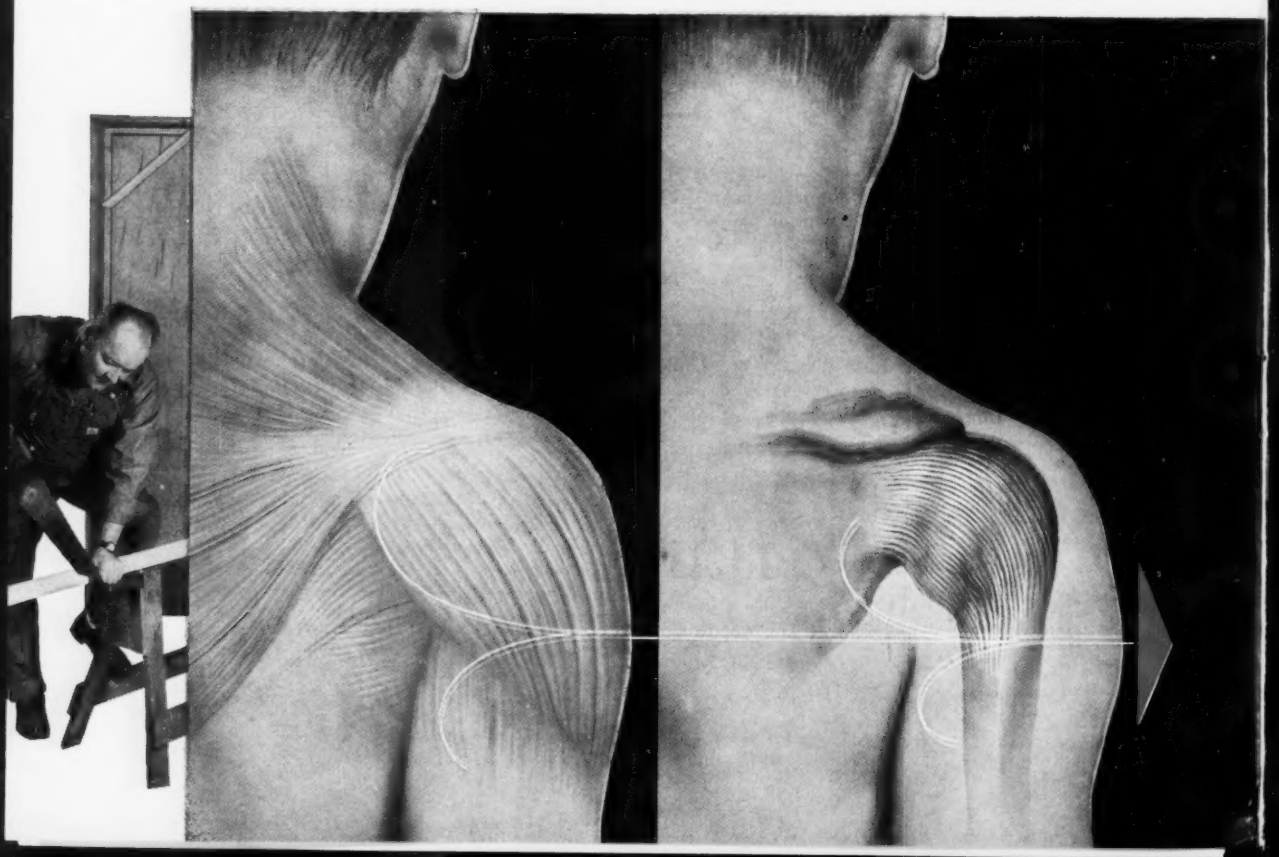


"Rheumatoid arthritis is a constitutional disease with symptoms affecting chiefly joints and muscles."[1] "Pain in the affected joint is accompanied by splinting of the adjacent muscles, with resultant 'muscle spasm.' "[2]



SELF-REGULATION IN MEDICINE

(Continued from Page 658)

changed residence, and then present his diplomas to the university at that city to have his privileges renewed. Usually he paid a fee and took another examination in order to demonstrate continuing proficiency in his art. If there were no university he presented his credentials to the city authorities. The fact that many cities, some of them large, had no university led to the establishment of medical oragnizations by government charter to carry out this licensing function. The Royal College of Physicians in London was so organized in 1518. At that time no person except a graduate of Oxford or Cambridge was allowed to practice in England unless he had been examined and approved by designated officers of this college. Scotland followed this example in 1617.

In later centuries the universities lost their high standing. Their standards became more unequal; medical science developed more and more outside the university, and there came to be more state interference in university affairs. By the 18th century the university degree was no longer a guarantee of fitness to practice medicine. Led by Prussia in 1725, states began to take from the universities the right to license and reverted to the situation obtaining in Italy at the time of Frederick II 500 years before. The medical faculties instructed according to a curriculum prescribed by the state and then examined the students for the degree. The state controlled the examination and issued the licenses without which no person could call himself a physician.

NEW RULING ON MEDICAL REDUCTIONS

Internal Revenue Service has clarified conditions under which expenses of travel, undertaken at a doctor's direction, may be deducted from taxable income. An elderly taxpayer, who was suffering from arteriosclerotic heart disease, had been advised by his doctor to go to a predetermined location where the temperature would be more suitable and where he could receive proper medical care. The physician also banned any further travel or sightseeing. Also, the physician advised the patient to have a nurse accompany him to administer the necessary injections and medications and to help him in and out of his wheelchair.

IRS ruled that because the travel was to alleviate specific ailments and was not for general improvement of health, the taxpayer was entitled to deduct his travel expenses and those of his nurse.—*AMA Washington News Letter.*

PUBLIC RELATIONS BEGINS IN THE DOCTOR'S OFFICE

Fourth installment of a paper by
R. WALLACE TEED, M.D., Ann Arbor
Chairman, MSMS Public Relations Committee

Doctors Must Communicate

The history and physical examination completed, the next step is in the field of communication. The patient wants to know what is wrong, and it is up to the physician to tell him this—in English. No one knows better than I how difficult this is, but it must be attempted. Many medical terms are derived from the Greek and Latin, and have, in addition, no common equivalents, but the physician must find some way of telling the facts in language that the patient can understand. In doing this, the meaning may be slightly distorted, but this is a lesser evil than leaving the patient in the dark. No patient complaint is more bitter than: "My doctor told me nothing."

To the busy physician, it may be sheer torture to sit down and explain step-by-step something which to him is mere routine, but it must be remembered that, to the patient, this may be the first introduction to a fearsome situation, and if he does not understand it, he questions whether the doctor does. He will frequently seek another physician, or perhaps a cultist, who will give him the information he seeks. I recently had a patient tell me, "Doctor, I have been examined by several physicians during the past four months, and this is the first time that anyone has told me anything about my trouble." This is not an uncommon experience.

After telling the patient what is wrong, the next step is to indicate what the treatment is to be. In many cases, the co-operation of the patient is essential for good results, and he cannot co-operate unless he knows why he is asked to do this or that. Sick people also may not remember details very well, and it may therefore be well to write down the various items advised so that nothing will be neglected.

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why PETN? *For cardiac effect:* PETN is ". . . the most effective drug currently available for prolonged prophylactic treatment of angina pectoris."[1] Prevents about 80% of anginal attacks.

why ATARAX? *For ataractic effect:* One of the most effective—and probably the safest—of tranquilizers, ATARAX frees the angina patient of his constant tension and anxiety. Ideal for the on-the-job patient. And ATARAX has a unique advantage in cardiac therapy: it is anti-arrhythmic and non-hypotensive.

why combine the two? *For greater therapeutic success:* In clinical trials, CARTRAX was demonstrably superior to previous therapy, including PETN alone. Specifically, 87% of angina patients did better. They were shown to suffer fewer attacks . . . require less nitroglycerin . . . have increased tolerance to physical effort . . . and be freed of cardiac fixation.

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*Trademark

1. Russek, H. I.: Postgrad. Med. *19*:562 (June) 1956.

Dosage and Supplied: Begin with 1 to 2 yellow CARTRAX "10" tablets (10 mg. PETN plus 10 mg. ATARAX) 3 to 4 times daily. When indicated this may be increased by switching to pink CARTRAX "20" tablets (20 mg. PETN plus 10 mg. ATARAX.) For convenience, write "CARTRAX 10" or "CARTRAX 20." In bottles of 100.

CARTRAX should be taken 30 to 60 minutes *before* meals, on a continuous dosage schedule. Use PETN preparations with caution in glaucoma.

MSMS Principle for Income Level Determination

By Max L. Lichter, M.D., Detroit

The problem of establishing income levels of subscribers for medical care insurance purposes has proved difficult of solution in the past. Methods used in connection with Blue Shield contracts have been unsatisfactory because they were based upon the family income averaged over a preceding three-year period and because there was no enforceable relationship between income and type of contract (so based) which was purchased. No method could be devised to determine in fact what a family's income might be since no positive method of ascertainment could be established. As a result much misunderstanding and attendant resentment flourished. Charges of bad faith were leveled at both physicians and patients.

In the past few years, much thought and study has been given to this crucial situation by the Michigan State Medical Society, Blue Shield and consumer groups. The House of Delegates Committee to Study Prepaid Insurance Plans recommended in 1957, that "the present method of determining income be re-examined." Two things were essential to an acceptable solution: (1) that income be realistically and readily established and designated, and (2) that a subscriber must obtain that contract into whose income limits his income fell.

These criteria have been fulfilled in the Principles of Medical Care Insurance as adopted by the House of Delegates of the Michigan State Medical Society on September 25, 1957. The pertinent statements are:

"The income level shall be determined by a projection of the current rate of earnings of the basic wage-earner in the family and not by the family income."

"Where the basic income is not readily determined and established (such as self-employed, farmers, salesmen on commission) the Committee on Medical Care Insurance of the Michigan State Medical Society shall develop appropriate criteria for determining eligibility for service benefits."

"The insurance carrier shall be responsible for classification of subscribers and appropriate designation of the Plan in which they must be enrolled. Income designation shall reflect the subscriber's current rate of pay projected on an annual basis. This designation shall be reviewed annually and changed as indicated by the review."

It was believed that since family income could not be established easily and with certainty it was fallacious to continue with the present method. The averaging method, further, could not take into account income fluctuations. But since employers must make payroll deductions based upon actual earnings for a variety of purposes, it was evident that this provided a positive approach to income determination related to medical care insurance. It was apparent that this could be readily done by employers.

The income designation then becomes simple to establish since it is to be "the current rate of pay projected on an annual basis," not how much an individual actually earned. For an hourly-rated employee a normal work year consists of 2080 hours. Thus, his income designation for this purpose would be his hourly rate multiplied by 2080. Overtime pay and shift premiums are not included since they represent inducements for the employee to extend himself beyond what is regarded as usual. On the other hand, if the employee worked less than 2080 hours in a year, as an example 1040 hours, this would not affect his income designation in terms of the definition adopted. Conversely, there would be no change if he worked more than a normal work year, such as 2500 hours. Both circumstances would average out any seeming advantages and disadvantages and thus remove income fluctuation as a complicating factor.

In the case of a salaried employee, the current rate of pay would be based upon the method of payment of the employer, i.e. weekly, semi-monthly, monthly. This would then be projected on an annual basis and income level designation established. Again, this would not reflect, necessarily, the actual earnings since they might be greater due to overtime pay and shift premiums; or they might be less if the amount of working time were less than a normal work year. It was believed that over a period of time these would average out.

It has been said that situations exist where someone in a family, for example the wife, might be employed at a wage greater than the basic wage-earner of the family—the husband. However, it must be conceded that when one considers the huge number of Blue Shield contracts in effect the percentage of such instances would be very small. To regard such an infrequent example as an inequity which must be considered in planning could lead only to complicating a greater problem which needs to be made less complicated.

It appears that no matter how much consideration and deliberation goes into planning, the proposed solution can be found to contain inequities. *The only logical solution is to recognize that inequities will exist and therefore that plan or proposal must be selected which has the fewest inequities when related to the total picture.* This is the approach which has been used in developing the new income level determination.

To compensate for possible inequities which might be envisioned, the fee schedules for the old income level contracts have been adjusted so that they reflect an overall increase of about 15 per cent. This figure happens to coincide with that

(Continued on Page 666)

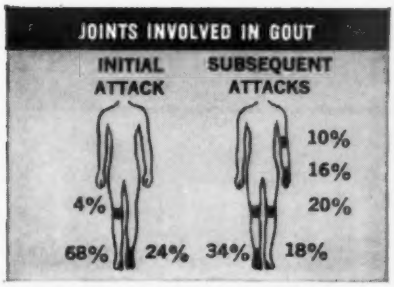
MSMS PRINCIPLE FOR INCOME LEVEL DETERMINATION

(Continued from Page 664)

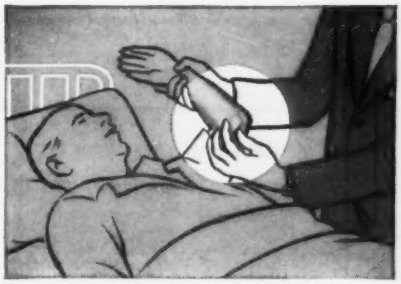
regarded as representing the average increase of family income over basic income. Since medical care insurance is based upon averages, and involves literally millions of people, it is evident that the new method does take into account the matter of family income, yet provides a more precise method of arriving at income designation.

Since physicians' fees traditionally have been based upon the "ability to pay" principle, the stipulation is made that a subscriber must enroll in that Plan into whose income level his projected earnings fall. It must be recognized that there must also be, on the part of the subscriber, an ability to pay the premium for his prepayment coverage. This recognition is consistent with medicine's traditional principle. It has been found that the cost of medical care insurance (Blue Shield) approximates its portion of the 4 per cent of the national gross income which an accepted survey indicated is spent annually for complete medical care (excluding drugs, prosthetic devices, glasses, et cetera). The payment of premiums represents a pooling of fiscal resources by patients to better enable them to meet the costs of medical care. This should, in no sense, be regarded as a departure from the "ability to pay" principle, at the risk of unrealistically increasing (and disproportionately so) the cost of medical care. The patient, then, has the responsibility of maintaining his part in our traditional principle by enrolling (even by requirement) in a commensurate plan. This circumvents opportunity for unhappiness resulting from additional charge over the service benefit because of inherent misunderstanding which could exist when an individual purchases a contract with a level less than his projected income. *Service benefit is the key to the strength of medicine's position in the medical care field.* The best way to maintain this strength is to combine and relate the role of the physician and the patient in the "ability to pay." This certainly cannot be regarded as compulsive in the sense of abridging a right.

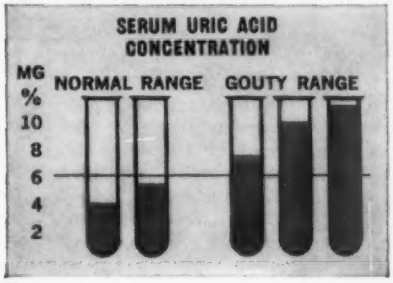
It is believed the new method is based upon logical grounds and that it is workable. If it be remembered that perfection has never been achieved, no serious objection can be made to any imperfection which upon reflection represents a very small percentage of the total. This method, which is a forward step, will go into effect with the new contracts to be offered by Blue Shield. Until some better solution is developed, it is essential that every physician in Michigan understand what is to be done in income level determination. It is essential that every physician in Michigan lend his sincere co-operation to make this effective. —*Detroit Medical News,* March 24, 1958.



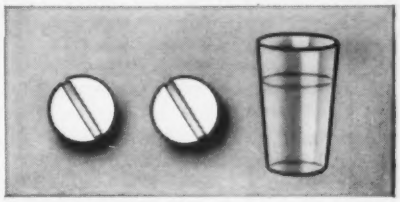
1. Recurrent joint pain followed by long periods of complete remission. *(Percentages refer to incidence.)*



2. Enlargement of bursae such as in this case involving the olecranon bursa.



3. Elevated serum uric acid levels.



4. Colchicine test: full dose (0.5 mg.) every 1 to 2 hours until pain is relieved or nausea, vomiting or diarrhea occur. The test requires usually 8 to 16 doses. Pain relief is highly indicative of gout.

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You and Your Business

CONFERENCE ON REHABILITATION OF PATIENTS IN THE GENERAL HOSPITAL

A conference on rehabilitation of patients in the general hospital was held at Kellogg Center, Michigan State University, East Lansing, May 14, 1958.

The objective of the conference was to inform and teach representatives of every service of a general hospital that might have anything to do with a rehabilitation program the broad, general concepts of rehabilitation and inspire them to go back to their respective institutions and spread the gospel, that rehabilitation need not be confined to a few highly specialized facilities in large cities, but should rather become, first, a type of philosophy that is applied to all patients and, second, a continuing constructive effort.

Michael M. Dacso, M.D., of New York City, Bellevue Medical Center, discussed the "Problem of Rehabilitation and its Solution." This keynote address ideally included the history, certain definitions, purposes, philosophy and progress for the future.

James W. Rae, M.D., of Ann Arbor, Michigan, discussed "Material Needed for Rehabilitation of General Hospital Patients." This presentation was concerned with the concept of the idea of aid to the handicapped and proceeded thence to the simpler gadgets which can be constructed by anyone with a little training and imagination and continuing on to the more complicated instruments necessary to do a more complete job.

Following the luncheon, Father Sudekamp, Secretary of Catholic Charities, Detroit, Michigan, addressed the group on the subject, "Restoration is At Least as Much a Matter of Spirit as of Body." To heal the one without the other is impossible. The crucial period is the time spent in the hospital—use that period to create in the mind, will power; neglect to use it and the heart of many a sufferer and of many a would be healer will break from sheer discouragement.

Max W. Newman, M.D., Detroit, Michigan, discussed "The Personnel Needs for the Rehabilitation of the Patients in a General Hospital." This talk dealt primarily with a listing of individuals needed but with those ideal characteristics that would make all those individuals who have contact with rehabilitation programs an asset rather than a liability. This talk also included the type of training necessary to produce these personalities.

Isidore J. Brightman, M.D., Albany, New York, Executive Director of the New York State Health Resources Board, presented the size of the rehabilitation problem, the impact economically on a community and the individual, and also discussed whether rehabilitation pays or not from the standpoint of the patient, the community and the hospital.

"NINE CANCERS WERE FOUND"

"Through regular examinations, we can uncover much unsuspected disease, can contribute to longevity, and can reduce disability," states Charles J. Tupper, M.D., Director of the University of Michigan periodic health appraisal program, just completed. The first year's results of the periodic examination program were "startling," says Doctor Tupper. Ages varied from forty-three to eight-seven years; all were professional people—most between fifty and sixty years of age.

Of 465 disease conditions or defects not previously recognized or known to exist; 245 were of such importance as to warrant immediate attention. Thirty-seven persons were found to have sugar diabetes, and twenty-one had hypertension. Among eight persons, nine cancers were found; one case of active tuberculosis was discovered, and two persons were found to have had heart attacks which were previously unrecognized.

DIFFERENCES BETWEEN THE WORLD MEDICAL ASSOCIATION AND THE WORLD HEALTH ORGANIZATION

Many physicians are not clearly aware of the distinctions between The World Medical Association (WMA) and the World Health Organization (WHO). There is also confusion as to the distinction between the United States Committee of WMA and the Citizens Committee for the WHO. Since WHO is to hold its "World Health Assembly" in the U.S.A. this spring, it would be desirable to have a clear understanding of these two organizations before this meeting.

The AMA is a member of WMA, and the AMA House of Delegates last June strongly urged every member of the AMA to join the U. S. Committee of WMA.

The World Medical Association

1. WMA is an organization of national medical associations. The unit of membership is the most representative national medical association in each country. It is completely non-governmental. It is not part of the U. N. It is a voluntary organization.

2. WMA represents the practicing medical profession.

3. WMA was organized in 1947 by AMA representatives and Western European medical leaders. Pur-

(Continued on Page 670)

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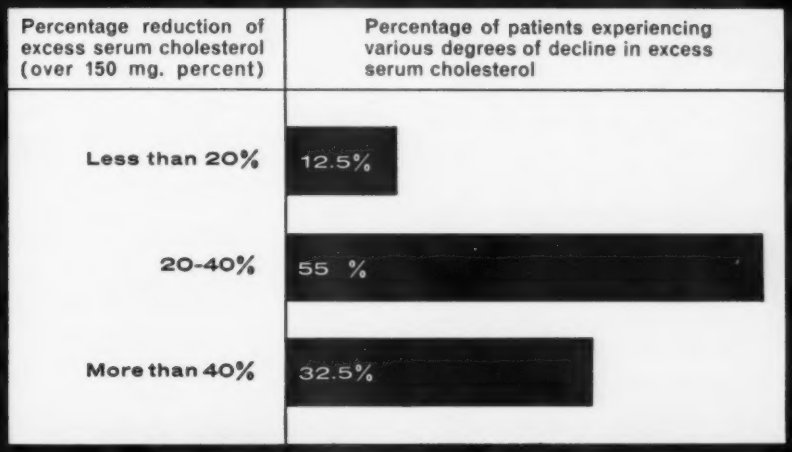

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May we send more complete information and bibliography?

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WMA AND WHO DIFFERENCES

(Continued from Page 668)

pose was to exchange medical knowledge, to protect the freedom of medicine, and promote world peace.

4. Each member association sends two delegates, two alternate delegates and observers to the General Assemblies—the supreme policy making body of WMA.

5. The executive body of WMA is the Council. This meets twice a year and comprises eleven members elected from the Assembly and the President, President-Elect and Treasurer.

6. WMA is supportd by members' dues and contributions and the annual budget is about $165,000.

7. American physicians and allied corporations interested in the work of WMA are organized as the United States Committee of The World Medical Association.

The World Health Organization

1. WHO is an intergovernmental health agency. The members are the governments that accept the nine principles upon which WHO is founded.

2. WHO represents governments in their public health and medical activities.

3. WHO is the result of proposal of U. N. in 1945 to create a specialized agency to deal with all matters related to health on a world-wide scale.

4. Each member government sends three delegates, chosen preferably from the national health administration of the government, to the annual World Health Assembly.

5. The Executive Board of WHO is the executive body and consists of eighteen members elected to represent eighteen member governments.

6. WHO is supported by dues allocated by the U. N. scale and the budget for 1958 is $13,000,000.

7. American citizens interested in the work of WHO are organized as the Citizens' Committee for the World Health Organization.

The World Medical Association membership gives you:

1. Friends all over the world.

2. The privilege of attending Annual Assemblies of WMA as an Official Observer for the U. S. Committee.

3. Introductions to professional leaders and medical institutions, wherever you may travel abroad.

4. Opportunities to participate in many programs for protection of the doctor's status in peace and war.

5. Aid and advice in travel arrangements for attendance at medical meetings abroad.

6. The *World Medical Journal*, and other newsletters and publications of WMA.

7. A membership certificate for display and a membership card.

Dr. Louis H. Bauer, Secretary-Treasurer
U. S. Committee, Inc., World Medical Association
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HIGHLIGHTS OF EXECUTIVE COMMITTEE OF THE COUNCIL

Meeting of March 18, 1958

- **Michigan Association of Professions.**—Another "First" for Michigan is being created: an association of the professions of medicine, law, engineering and architecture. Continued organizational activity of MAP was authorized and monthly progress reports are to be presented to The Council and its Executive Committee.
- **Site for New MSMS Building.**—Preliminary purchase agreement for a site on Saginaw Street (M 78) and Abbott Road in East Lansing was amended, upon recommendation of Legal Counsel Lester P. Dodd, and the President, Secretary, and Chairman of The Council were authorized to sign this agreement with Green Realty Company of Lansing.

  Contract with the architect (Yamasaki, Leinweber & Associates) also was authorized to be signed by the President and Secretary.
- **Michigan Hospital Service Progress Report.**—Brooker L. Masters, M.D., Medical Director of MHS, outlined problems facing Blue Cross, and urged maximum co-operation between medical hospitals of Michigan and doctors of medicine.
- **Monthly Financial Reports** were studied and approved; bills payable were approved, and payment was authorized.
- **A Special Membership Form,** to be used in the MSMS House of Delegates when presenting nominations for Life, Retired, Associate, and other, memberships, was presented by Speaker K. H. Johnson, M.D., and approved.
- **Appointments.**—John R. Rodger, M.D., Bellaire, was authorized to attend as MSMS representative the Regional Traffic Safety Conference in Chicago April 1-2; D. W. Heubner, M.D., Hastings, was appointed a member of the MSMS Legislative Committee; E. G. Kiehler, M.D., Lapeer, was appointed a member of the MSMS Public Relations Committee; Clifford L. House, M.D., Lapeer, was appointed a member of the MSMS Rheumatic Fever Control Committee; Otto O. Beck, M.D., Birmingham, W. B. Harm, M.D., Detroit, and J. W. Logie, M.D., Grand Rapids, were nominated by MSMS to fill vacancies on the Board of Trustees of Michigan Hospital Service (Blue Cross); L. Fernald Foster, M.D., Detroit, and B. M. Harris, M.D., Ypsilanti, were reappointed as MSMS consultants to the University of Michigan Study Group on Blue Cross-Blue Shield; C. A. Behney, M.D., was appointed MSMS representative to AMA Conference on Perinatal Mortality, Chicago, March 23; Max

(Continued on Page 672)

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HIGHLIGHTS OF THE COUNCIL

(Continued from Page 670)

K. Newman, M.D., Detroit, and J. W. Rae, M.D., Ann Arbor, appointed MSMS representatives on Michigan Welfare League Committee on Rehabilitation Services; G. B. Saltonstall, M.D., Charlevoix, appointed Chairman of Committee on Committees, with George W. Slagle, M.D., Battle Creek, as a member thereof.

- **Committee Reports.**—The following reports of MSMS and Council committees were given consideration: (1) Committee on Prevention of Highway Accidents with Chairman John R. Rodger, M.D., Bellaire, and Dr. C. W. Muehlberger of the State Health Department Laboratory present; (2) Ad Hoc Committee on Medicare, minutes of February 20; (3) Mental Health Committee, January 30; (4) Maternal Health Committee, February 6; (5) Rheumatic Fever Control Committee, February 12; (6) Committee on Blue Cross Payments for Services of Pathologists, February 12; (7) Child Welfare Committee, February 13; (8) Study of Insurance Programs for MSMS Members, February 26; (9) Tuberculosis Control Committee, March 5; (10) National Defense Committee, March 12; (11) Venereal Disease Control Committee, March 13; (12) Medical Care Insurance Committee, meeting of March 1-2.
- **Legal Counsel Dodd's Monthly Report** included opinions on question of practitioners authorized to serve in county tuberculosis hospitals; re patient signing release form in regard to hospital chart; and on the question of payment for EKG's to laboratory.
- **Michigan Clinical Institute.**—A vote of thanks was extended to all who helped make this March 19-21 meeting in Detroit a great success, with a total registration of 2,886.
- **Public Relations Counsel Monthly Report** included (a) *Analysis of current legislation in the Michigan Legislature;* (b) *Ambulance Driver Training.*—Action by the 1957 MSMS House of Delegates had been referred to the ambulance section of the Michigan Funeral Directors Association which shortly will incorporate in its public relations section an educational program for ambulance drivers and assistants; further an article on ambulance driver training will appear shortly in *The Michigan Funeral Director,* the house organ of the MFDA; (c) *Authority to reprint 10,000 copies of "In Planning Your Career,"* a very popular brochure of the Michigan State Medical Society, was given; (d) *"Education in Medicine and Nursing in Michigan"* is the title of Staff Study No. 3 under the Survey of Higher Education in Michigan, carried out by the Michigan Legislative Study Commission on Higher Education in which MSMS co-operated.

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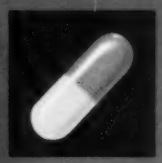

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Acetophenetidin . . . . . gr. 2½
Aspirin (Acetylsalicylic Acid) . . . . . gr. 3½
Caffeine . . . . . gr. ½

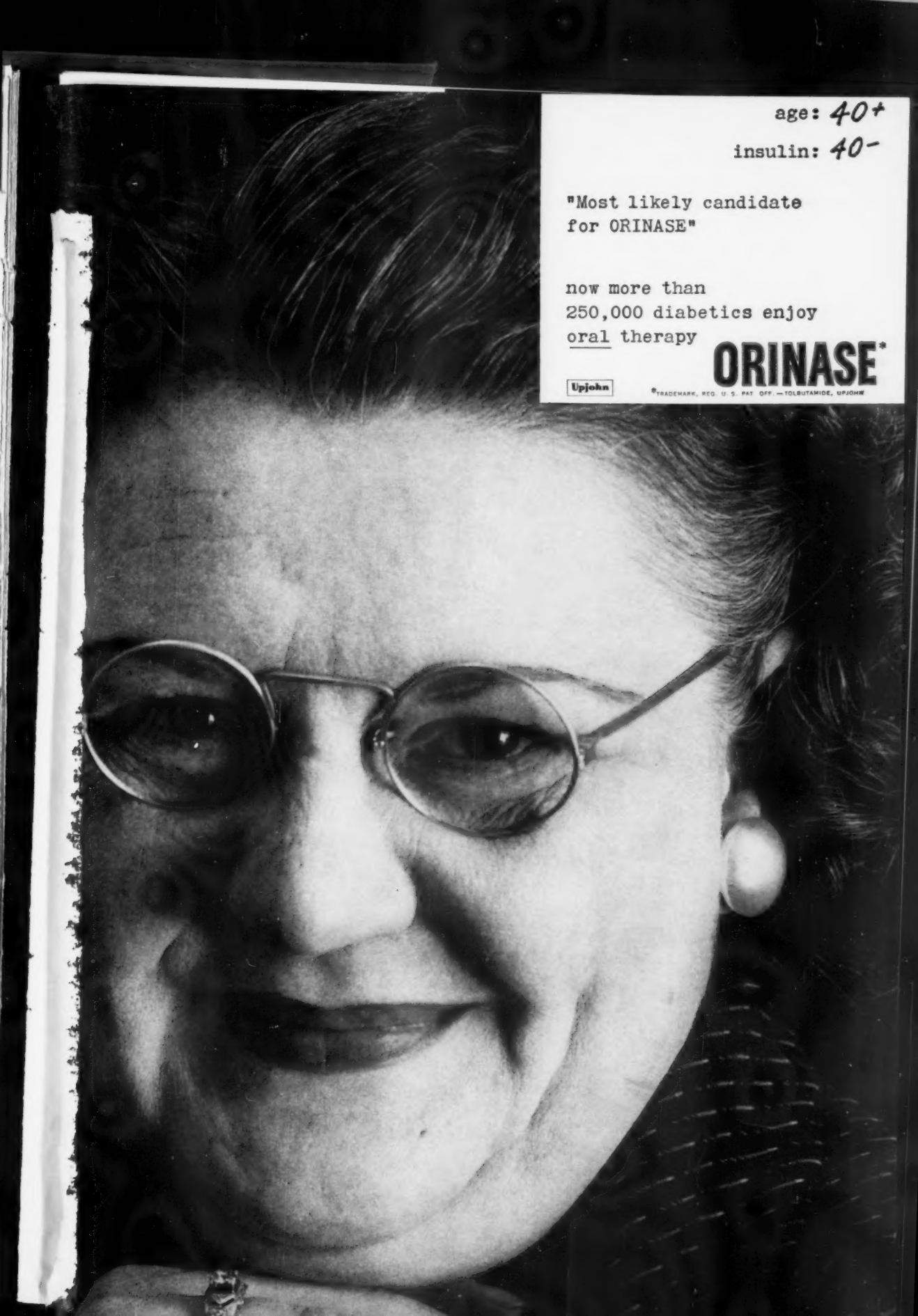
...from mild pain complicated by tension and restlessness.

'EMPIRAL'®

Phenobarbital . . . . . gr. ¼
Acetophenetidin . . . . . gr. 2½
Aspirin (Acetylsalicylic Acid) . . . . . gr. 3½

*Subject to Federal Narcotic Regulations

BURROUGHS WELLCOME & CO. (U.S.A.) INC., Tuckahoe, New York


age: 40+
insulin: 40-
"Most likely candidate
for ORINASE"
now more than
250,000 diabetics enjoy
oral therapy
ORINASE*
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AMEF CHAIRMAN STATES CASE FOR PHYSICIAN SUPPORT

Every physician earning his livelihood due to the possession of a medical degree, owes an incalculable and never ending debt to his medical school. Increased costs of operation of our eighty-five medical schools are surpassing the amount obtained through taxes and endowments.

It is estimated that over two hundred million dollars are required for operating expenses each year. So far, the AMEF has only been able to raise and contribute one-half of one per cent of this amount.

The State of Michigan with approximately 6,000 physicians contributed less than ten thousand dollars last year, or only 1/100th of the million raised. This represents approximately one-and-a-half dollars for each doctor in the state, whereas $10 should be the absolute minimum. Nine states have solved this problem by an increase in state dues ranging from $5 to $20. Even a $10 levy in Michigan would produce $60,000, or over six times what is now contributed.

Only 44,000 doctors participated last year. If one hundred thousand doctors contributed $100 each, ten million needed dollars would be raised. We can rest assured if this money is not contributed by doctors, our Federal Government will allocate the necessary funds and, inevitably, Federal control over our medical schools will be increased.

The AMEF provides the mechanism through which individual members of the medical profession can shoulder their share of the support of our medical education system. The AMA underwrites all costs of promotion and administration of the Foundation. Thus, AMEF is one of the few organizations raising money where the entire income goes to the cause for which contributions are given.

Doctors have felt generally that the voluntary method of giving should be preserved. Recent experience in Wayne County during our Building Fund Drive, indicates only about 50 per cent of the membership will contribute adequately on a voluntary basis.

If our medical schools are to preserve some semblance of freedom from Federal control, the physicians of America must drastically increase their contributions to the AMEF. All physicians of Michigan should, in their own best interest, make as an absolute minimum a $10 contribution to this fund. Checks should be made payable to the AMEF and mailed to 535 North Dearborn Street, Chicago, Illinois. A physician may specifically earmark his contribution for the medical school of his choice.

Any amount you give is tax deductible. Make a contribution now toward the debt you can never fully repay.

—F. P. Rhoades, M.D.
AMEF Chairman for Michigan

MY DAD— HE HURT HIS BACK REAL BAD

"It happened at work while he was putting oil in something"

"He told Mom his shoulder felt like it was on fire"

"He couldn't swing a bat without hurting"

"But Doctor gave him some nice pills--and the pain went away fast"

"Dad said we'd play ball again tomorrow when he comes home"

AND THE PAIN WENT AWAY FAST

FOR PAIN

Percodan®

(Salts of Dihydrohydroxycodeinone and Homatropine, plus APC) **TABLETS**

ACTS FASTER...
usually within 5-15 minutes

LASTS LONGER...
usually for 6 hours or more

MORE THOROUGH RELIEF...
permits uninterrupted sleep through the night

RARELY CONSTIPATES...
excellent for chronic or bedridden patients

and now... **NEW**

Percodan®-Demi

VERSATILE

New "demi" strength permits dosage flexibility to meet each patient's specific needs. PERCODAN-DEMI provides the PERCODAN formula with one-half the amount of salts of dihydrohydroxycodeinone and homatropine.

AVERAGE ADULT DOSE: 1 tablet every 6 hours. May be habit-forming. Available through all pharmacies.

Each PERCODAN® Tablet contains 4.50 mg. dihydrohydroxycodeinone hydrochloride, 0.38 mg. dihydrohydroxycodeinone terephthalate, 0.38 mg. homatropine terephthalate, 224 mg. acetylsalicylic acid, 160 mg. phenacetin, and 32 mg. caffeine.

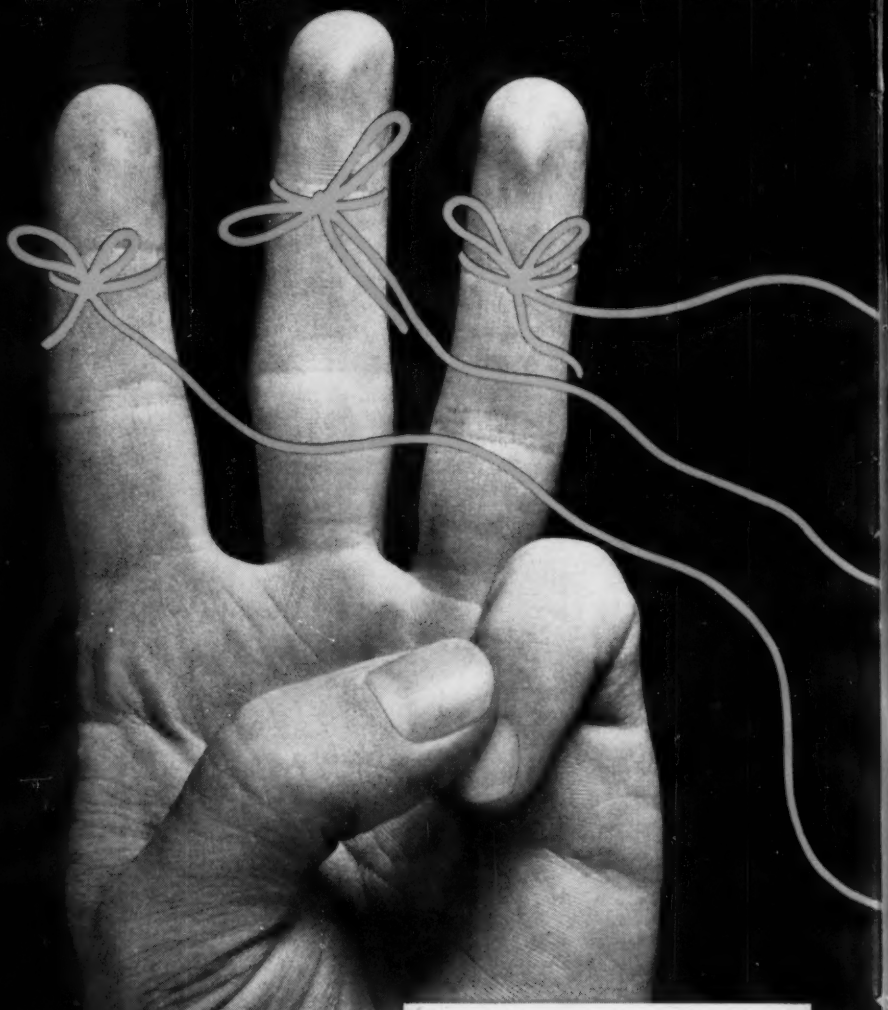
Literature? Write

Endo® **ENDO LABORATORIES**
Richmond Hill 18, New York

*U.S. Pat. 2,628,185

When tetracycline therapy is indicated–

3 INDISPUTABLE POINTS



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Bristol

TO REMEMBER ABOUT

Tetrex®

THE ORIGINAL TETRACYCLINE PHOSPHATE COMPLEX

U.S. PAT. NO. 2,791,609

1 Tetrex requires no "activating additive"

– it is purely tetracycline phosphate complex, with an inherent, chemically unique property of being rapidly and efficiently absorbed.

Each Tetrex Capsule contains:

Active ingredient: TETRACYCLINE PHOSPHATE COMPLEX, 250 mg. (tetracycline HCl activity)

Excipient: Lactose q.s.

2 Tetrex produces "peak high" tetracycline serum levels

– over 5000 human blood determinations after oral or intramuscular administration have consistently demonstrated fast, high, prolonged serum levels in patients of all ages.[3,5,6,7,8,9,10,11,12,13,14,15]

3 Tetrex has an impressive documented record of clinical effectiveness

– more than 170 million doses of tetracycline phosphate complex in 1957, with 5 published clinical reports by 9 investigators on 826 patients.[3,5,7,8,10] *Clinical evaluation:* "should probably be considered an improvement over, and an ultimate replacement for, the older tetracycline hydrochloride."[10]

BRISTOL LABORATORIES INC., Syracuse, New York

BLUE SHIELD—AMERICA'S UNIQUE CONTRIBUTION

In these days of instantaneous communication and over-night travel to the most remote places in the world, few nations can claim any social ideas or innovations as exclusively their own.

But the fact is that in the field of medical economics, American medicine has produced a program that is uniquely American. There is nothing comparable to Blue Shield in any other nation today.

Specifically, in no other country has the medical profession been able to develop a non-profit plan for medical care prepayment in which the participation of both patient and doctor is voluntary, there is complete freedom of choice for doctor and patient, services are paid for on a fee-for-service basis with the payments subject to medical control, there's no third party to regulate the doctor's practice, and no governmental agency has contributed one cent of direct subsidy to the program.

As a spokesman for the World Medical Association, the "international voice of organized medicine" representing 750,000 physicians in 53 nations of the "free world," said recently: "American physicians are singularly fortunate in having met their social and economic problems by voluntary action, turning back the threat of political domination."

Of course the plain fact is that although physicians have *met* their social and economic problems, they are still a long way from *solving* them. Through their own Blue Shield program, and with the help of the many commercial insurance companies that have followed the trails blazed by Blue Shield, physicians have made a strong and substantial beginning toward providing basic medical care security for all of their patients.

But there are big and difficult problems yet to be solved—in the care of long term and chronic illness, the aged, the rural populations, the indigent, etc.

Blue Shield offers us a unique instrument with which to tackle these problems. Whether or not it will yet suffice to save America from resorting to the state socialism and the compulsory solutions that most other countries have adopted will probably depend on the vision and energy and public spirit which every doctor brings to the support and guidance of his own Blue Shield Plan.

The death rate from cardiovascular disease, which now claims one out of every two American lives, varies from state to state, according to a new publication, *Patterns of Disease*, prepared by Parke, Davis & Company for the medical profession. The new England states rank first in heart disease death rates and the southwestern states are at the bottom of the list, according to the publication.

AMA Washington Letter

THE MONTH IN WASHINGTON

The recession continues to influence the course of much legislation, as Congress points toward the windup of its session. Even in the health fields, bills that promise in one way or another to alleviate unemployment appear to have priority. At the same time, federal departments are favoring construction grants to projects that can be started without much delay.

In legislation, here are some of the developments:

1. Liberalizations in unemployment compensation and in social security are receiving constant attention on Capitol Hill. At this writing, the bill to extend the period for unemployment compensation payments is making progress. There is the possibility also that it will make participation mandatory for all employers.

Prominent among proposed changes in the social security program itself is the Forand bill for free hospitalization and in-hospital medical care and surgery for persons entitled to social security benefits. It is being pushed by the AFL-CIO and by some liberal Democrats, and opposed by the American Medical Association and a growing group of other organizations. The opposition is convinced that the Forand bill is unnecessary, that it would be far more costly than anticipated, and that it would point the way to a broad national medical care plan for all persons covered by social security.

2. A controversial bill to vastly increase money available for grants for community facilities—waste plants, hospitals, state medical schools included—is active in Congress. One proposal is to vote a billion dollars, to be lent out (at about 3½% interest for 50 years) to communities. The objective here, as in many other measures, is to put people to work on construction projects.

Federal agencies have evolved a number of schemes to get U.S. dollars into circulation faster, and are attempting to work out others. In each case described below, no additional appropriation is involved; money is shifted from a project that is getting a slow start to one that is about ready to begin construction. Also, all totals given represent amounts to be spent by the sponsors as well as the federal government. Here are arrangements already made:

1. In January, the Hill-Burton hospital construction program called for U.S. grants to start buildings valued at $381 million; this figure has been stepped up to $405 million by July 1.

2. Between January and July 1, the original plan was to allocate enough money to start $120 million in construction for health research plants. This has been increased to $182 million.

3. Before the recession became so prominent an issue, the plan was to grant enough U.S. money to start construction of $170 million in sewage plants. Under pressure, the total has been increased to $215 million.

In most cases, when a project is delayed and thus loses its allocation, the grant is re-scheduled for next fiscal year.

* * *

American Medical Association is one of the four sponsors of a new Joint Council to Improve the Health Care of the Aged. Others are American Dental Association, American Hospital Association and American Nursing Homes Association.

The council already has authorized research in a number of directions to (a) analyze the health needs of the aged, (b) appraise available health resources for them, and (c) develop the best possible health care for them, regardless of their economic status.

Effects of this united front action should be felt when Congress takes up the Forand bill and other legislation pointed toward relief for the aged.

* * *

American Medical Association is asking Congress to strengthen the Civil Aeronautics Administration's medical department so it can properly supervise fliers' physical examinations and advise on other aviation medical matters. AMA also is recommending that an office of civil air surgeon and a medical research laboratory be established within CAA.

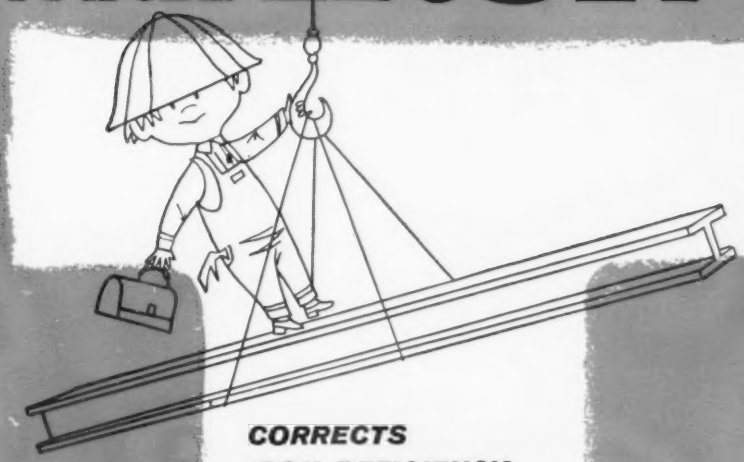
Congress has under consideration several plans for reorganizing the Defense Department, two of which would result in elimination of the office of Assistant Secretary for Health and Medical matters.

Andrew Biemiller, top legislative man for the AFL-CIO, told a recent delegation just returned from visiting Capitol Hill: "Congressmen are falling all over themselves in wanting to do something in the recession. I think we can cash in on this."

Medicare is working up a new claim form that will have a check-list of common errors on the back; this is intended to eliminate much correspondence now necessary when the physician makes an error on the form.

new INCREMIN* with IRON syrup

LYSINE-VITAMINS



CORRECTS IRON DEFICIENCY AS IT STIMULATES APPETITE

DELICIOUS CHERRY FLAVOR
DESIGNED TO APPEAL TO
BOTH CHILDREN AND ADULTS

PARTICULARLY FOR CHILDREN

Supplies essential Iron as ferric pyrophosphate, highly stable, well-tolerated, readily absorbed; essential vitamins B_1, B_6 and B_{12}, established as appetite stimulants; essential l-Lysine for greater protein economy in the pediatric diet.

INCREMIN Syrup

FORMULA: Each teaspoonful (5 cc.) contains:

l-Lysine HCl	300 mg.
Ferric Pyrophosphate (Soluble)	250 mg.
Iron (as Ferric Pyrophosphate)	30 mg.
Vitamin B_{12} Crystalline	25 mcgm.
Thiamine Mononitrate (B_1)	10 mg.
Pyridoxine HCl (B_6)	5 mg.
Alcohol	0.75%

Average dosage is 1 teaspoonful daily.
Available in bottles of 4 fl. oz.

*REG. U. S. PAT. OFF.

LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY, PEARL RIVER, N.Y.

AMA News Notes

TWO CIVIL DEFENSE PROGRAMS SCHEDULED IN SAN FRANCISCO

Two medical civil defense meetings will be held in San Francisco immediately preceding the American Medical Association's 107th Annual Meeting. On June 19-20, the 12th Naval District will sponsor a symposium on "Medical Problems of Modern Warfare and Civil Defense" at the U.S. Naval Radiological Defense Laboratory, and on June 21 the AMA's Council on National Defense will sponsor its 6th Annual National Medical Civil Defense Conference in the Sheraton-Palace Hotel. Dr. David B. Allman, AMA president, and Frank W. Barton, secretary, AMA Council on National Defense, will speak at the naval symposium on the plan and activities of organized medicine for medical preparedness in disasters or in the event of all-out war.

Dr. Gunnar Gundersen, AMA president-elect, will welcome participants to the AMA's civil defense meeting on June 21. The current federal civil defense program, including the national plan for mobilization of resources (personnel, facilities, supplies) will be outlined during the morning session by officials of federal governmental agencies involved. Also scheduled for the morning session will be a discussion of the threat and impact of newer weapons and delivery systems by an outstanding military planner, and a report on the legislative program now pending before congress for a national survival plan by the Hon. Chet Holifield, U.S. congressman, 19th district of California.

During the afternoon, the Surgeons-General of the Army, Navy, Air Force and Public Health Service will discuss the civil defense role and responsibilities of civilian physicians. Two other subjects to be covered include the radioactive fall-out problem and the feasibility of a national shelter program.

All physicians interested in civil defense planning are urged to attend these two worthwhile meetings.

NEW EXHIBITS FOR THE PUBLIC

The AMA Bureau of Exhibits announces that a number of new exhibits will be ready for showings by local medical societies at fairs, home shows, school and similar public gatherings this spring and summer.

You Can Reduce—shows foods to fill up on and stay away from; gives visitor an opportunity to check his weight on the scales; presents answers to pertinent questions on reducing; pictures 25 different foods and the number of calories in the servings shown.

Food and Nutrition Quackery—developed in co-operation with U.S. Food and Drug Administration, Post Office Department's fraud division, and National Better Business Bureau to point up the major false claims made in the promotion of food products and nutrition ideas; exposes house-to-house peddlers of "food supplements," nutrition and health lecturers and so-called "experts;" displays various reducing aids on a roulette wheel; features special "buyer beware" section explaining how public can recognize food quacks and their claims.

Breathing—presents the anatomy of body's breathing system and air passages and location of lungs in the body; viewer can observe how lungs expand and contract and the movement of the rib cage.

Glands—shows the location and functions of various glands in the body; presents three-dimensional models of glands.

Poisoning of Children—demonstrates dangers of common household products and depicts those products that are leading causes of poisonings in children at home.

Health Appraisal of the School Child—highlights principal health appraisal procedures, such as teacher observation, screening procedures, dental and medical examinations and the follow-through.

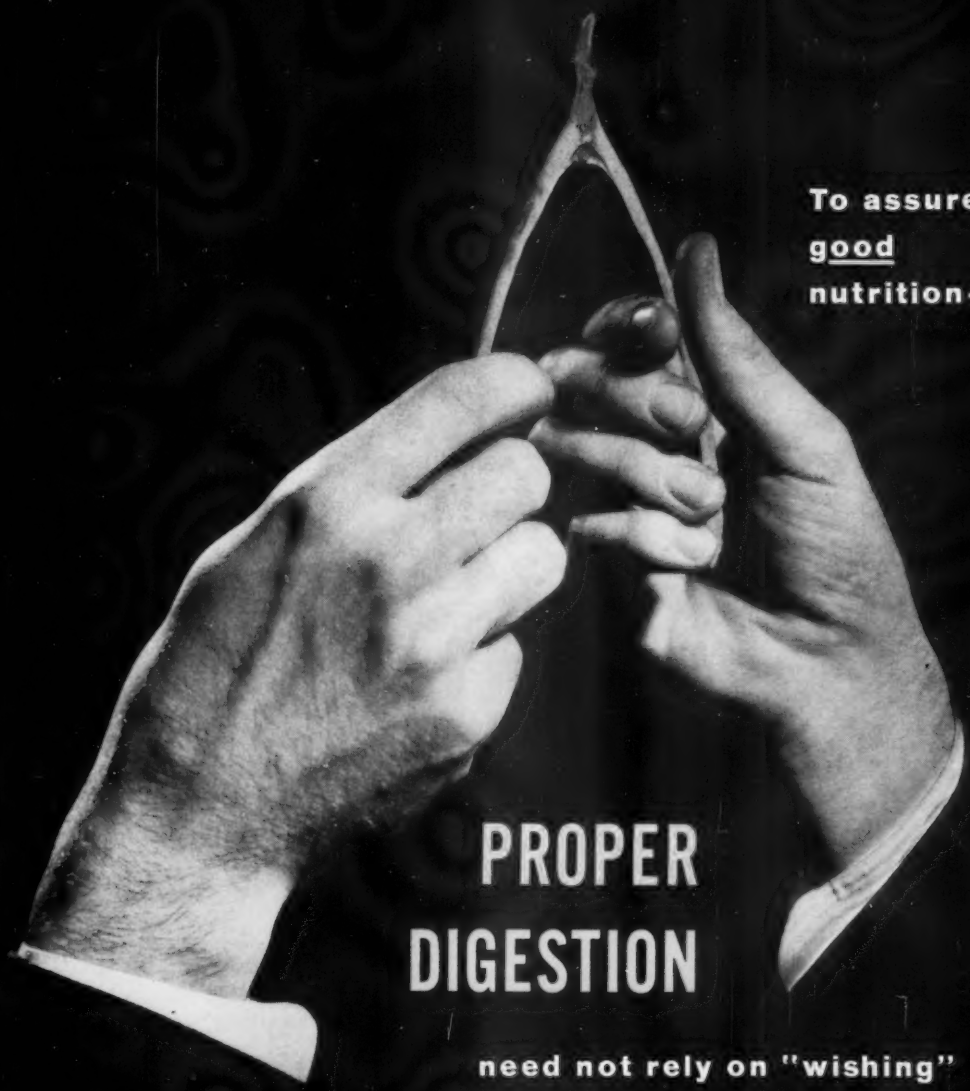
PROTECTING THE HEALTH OF THE HIGH SCHOOL ATHLETE

Curbing the number of unnecessary high school sports injuries and deaths is a community challenge. Physicians can provide the needed local leadership by working with school officials, coaches association, parent-teacher groups and dental society to develop adequate school health and safety programs for sports participants. One practical method—discussed in a new American Medical Association pamphlet—calls for the sponsoring of high school sports injury conferences. Purpose of these conferences is to instruct coaches, athletic directors and team physicians on the early recognition of injuries, appropriate first aid measures and the prompt referral of injured players for medical or dental care. Entitled "Protecting the Health of the High School Athlete," the booklet was prepared under the auspices of the AMA's Committee on Injury in Sports. Further information and copies of the booklet may be secured from the AMA's Bureau of Health Education.

PAMPHLET ON DRIVER FITNESS

Before taking the wheel, every driver should check to make sure that he's fit to drive. Under certain circumstances—outlined in a new American Medical Association pamphlet—a driver can be a dangerous hazard on the road. "Are You Fit to Drive?" urges drivers to contact their physicians if they are in doubt about their fitness. Prepared by the AMA's Committee on Medical Aspects of Automobile Injuries and Deaths in co-operation with the Center for Safety Education at New York University, the booklet contains information about those conditions that can adversely affect driving skills—emotional upsets, driver attitudes, sleepi-

(Continued on Page 686)



To assure good nutrition—

PROPER DIGESTION

need not rely on "wishing"

Each double-layered Entozyme tablet contains:

Pepsin, N.F. 250 mg.
—released in the stomach from gastric-soluble outer coating of tablet.

Pancreatin, U.S.P. 300 mg.

Bile Salts 150 mg.
—released in the small intestine from enteric-coated inner core.

A. H. ROBINS CO., INC.
Richmond 20, Virginia
Ethical Pharmaceuticals of Merit since 1878

As a comprehensive supplement to deficient natural secretion of digestive enzymes, particularly in older patients, ENTOZYME effectively improves nutrition by bridging the gap between adequate ingestion and proper digestion. Among patients of all ages, it has proved helpful in chronic cholecystitis, post-cholecystectomy syndrome, subtotal gastrectomy, pancreatitis, dyspepsia, food intolerance, flatulence, nausea and chronic nutritional disturbances.

For comprehensive digestive enzyme replacement—

ENTOZYME®

Robins

PAMPHLET ON DRIVER FITNESS

(Continued from Page 684)

ness, medicines, faulty vision, certain nerve and heart disorders, diabetes, old age and drinking.

For distribution through physicians' offices, the booklet currently is available from the Association of Casualty and Surety Companies, 60 John Street, New York 38, N. Y. Price is $4.60 per 100 copies, regardless of quantity.

REFERRAL CENTERS FOR CHRONICALLY ILL SURVEYED

A survey of five information and referral centers for the chronically ill currently is being conducted by the AMA's Council on Medical Service. Located in Chicago, Cleveland, Milwaukee, San Francisco and Essex county, N. J., these centers operate as central clearing houses for information on existing facilities for the care of chronically ill in the community. Such centers usually maintain complete information on rates, eligibility, requirements and services offered by nursing and old-age homes, chronic institutions, social service agencies, rehabilitation facilities and other services, and often carry on research to evaluate unmet needs for care in the area.

The Council's report on these centers should be of interest to physicians concerned with chronically ill patients. Any information on similar centers in other communities will be welcomed by the Council.

DOCTORS' WIVES PLAN JUNE CONVENTION

The call of the west will be heeded by physicians' wives as they travel to San Francisco in June for the thirty-fifth annual convention of the Woman's Auxiliary to the American Medical Association at the Fairmont Hotel. National committee meetings and round table discussions will be held June 21-23 with formal opening of the convention slated for Tuesday morning, June 24. An interesting and varied program is being arranged by co-chairmen Mrs. Matthew N. Hosmer, San Rafael, and Mrs. Samuel R. Sherman, San Francisco, California.

Business sessions on Tuesday and Wednesday will be devoted to state and national committee reports and discussions on current projects. Tuesday's luncheon in honor of past presidents will feature guest speaker Mr. Richard H. McFeeley, principal of George School, Bucks county, Penna. Speaker at Wednesday's luncheon in honor of the president (Mrs. Paul C. Craig of Pennsylvania) and the president-elect (Mrs. E. Athur Underwood of Washington) will be Dr. David B. Allman, immediate past president of the AMA. At this session Mrs. Craig will present the Woman's Auxiliary contribution to the American Medical Education Foundation, and Dr. George F. Lull, AMEF president, will present AMEF awards to the auxiliaries.

Election and installation of national officers will be held Thursday morning with adjournment scheduled for noon.

One of the highlights of the convention will be the premiere showing of the new recruitment film, "Helping Hands for Julie," at 3 p.m. Wednesday. Produced by the AMA, the American Hospital Association and E. R. Squibb and Company, the film is designed to encourage young people on medical health careers. All Auxiliary members, their husbands and friends, career guidance counselors and members of allied medical groups are invited to attend this showing.

MEETING ON LABELING OF CHEMICALS

As part of an over-all program to prevent poisonings and to increase public awareness of the hazards of certain chemical products, the AMA's Committee on Toxicology has drafted a broad model law requiring precautionary labeling of hazardous substances in commercial, household and industrial chemicals. The bill is intended as a model for uniform laws to require the declaration of hazardous ingredients and warning statements on the label and in the accompanying literature of chemical products.

The first of two or more conferences with representatives of health departments, regulatory agencies, medical societies and allied health organizations to discuss this and other tentative legislation will be held May 9 at AMA headquarters, Chicago. The Conference on Labeling Hazardous Substances will focus attention on the nature of the general problem as seen by the public, the medical profession, regulatory officials and trade associations, and also will provide discussion on both local and federal labeling laws.

Newscopes—Reprints of a report of the AMA Committee on Medical Rating of Physical Impairment which appeared in the March 1 issue of the *Journal of the AMA* currently are available from the Council on Medical Service. The article calls attention to the substantial increase in consultative examinations being purchased with federal funds by state agencies administering the Old-Age and Survivors Insurance Disability program, lists purposes for which consultative examinations may be authorized and contains a roster of state medical consultants and reviewing physicians as listed by the Bureau of Old-Age and Survivors Insurance. . . . AMA Bureau of Health Education announces that *"Health Magazine of the Air"* was distributed to 450 radio stations in March. Monthly spot announcements to be narrated by Douglas Fairbanks, Jr. in April and Ralph Bellamy in May. . . . The ninth annual *"Reviews of Medical Motion Pictures,"* containing all film reviews published in the *Journal of the AMA* during 1957, now is available from the AMA's Film Library.

PRESIDENT ISSUES ORDER ON DRAFTING OF DOCTORS

The President has signed an executive order whose tardiness has no practical significance. It simply authorizes Defense Department to activate Reserve doctors who are subject to Selective Service call-up. This is a routine step based on Congressional amendment of the draft laws last June. As long as armed forces continue to get sufficient medical and dental volunteers to fill their needs, it won't be necessary for The Secretary of Defense to invoke this delegation of power.

WANTED

BY ALL DERMATOLOGISTS

A TOPICAL "METI" STEROID PREPARATION FREE FROM UNWANTED SENSITIZATION POTENTIAL

NAME **METI-DERM® CREAM 0.5%**

DESCRIPTION 5 mg. prednisolone, free alcohol, in each gram—nonstaining, water-washable base—exerts a therapeutic effect in presence of an exudate without being occlusive.

supplied: 10 Gm. tube.

Meti—T.M.—brand of corticosteroids.

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14. Robinson, H. M., Jr.; Robinson, R. C. Cohen, M. M.: U.S. Armed Forces M. J.
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23. Frank,
24. Mulli H. M.,
25. Weidm *74*:58,

METI-DERM Cream 0.5% and Neomycin, 10 Gm. tubes.

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- no edema
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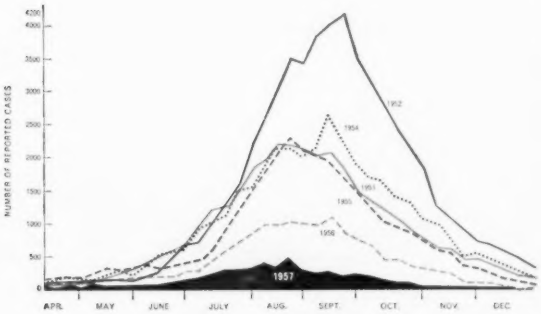
TION IN TOPICAL CREAM METI-DERM Cream ory, antiallergic action in the affected area. No system ention, edema and weight gain, have been reported wi

—HASTENS RECOVERY After local application of flatten and fade; edema, erythema and infiltration dim

A MIRACLE IN OUR TIME?

At the last accounting,[1] physicians throughout the country had administered at least one dose of poliomyelitis vaccine to 64 million Americans—all three doses to an estimated 34 million. Undoubtedly, these inoculations have played a major part in the dramatic reduction of paralytic poliomyelitis in this country.



Incidence of polio in the United States, 1952-1957
(data compiled from U.S.P.H.S. reports)

vaccine is plentiful for the job remaining

There are still more than 45 million Americans under forty who have received no vaccine at all and many more who have taken only one or two doses.

As it was phrased in a public statement by the Department of Health, Education, and Welfare:

> *"It will be a tragedy if, simply because of public apathy, vaccine which might prevent paralysis or even death lies on the shelf unused."*[2]

Eli Lilly and Company is prepared to assist you and your local medical society to reach those individuals who still lack full protection. *For information see your Lilly representative.*

1. J. A. M. A., 165:*21 (November 23), 1957.*
2. Department of Health, Education, and Welfare: News Release, October 10, 1957.

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The JOURNAL

of the Michigan State Medical Society

Issued Monthly Under the Direction of the Council

VOLUME 57 May, 1958 NUMBER 5

Active Immunization Against Tuberculosis

By W. J. Nungester, M.D.
Ann Arbor, Michigan

DURING the past seventy-five years, since the discovery by Koch of the cause of tuberculosis, many attempts have been made to increase man's resistance to this infectious disease by active immunization with various types of vaccines. Many experiments have been made in animals with the hope of developing an effective vaccine. Studies on man and animals dealing with the pathogenesis of the disease have been both instructive and confusing in terms of indicating a possibility for successful active immunization. In early studies, Koch demonstrated that an animal with an existing lesion reacted quite differently to reinoculation of virulent tubercle bacilli than did a normal animal. The infected animal rejected the second inoculation of virulent organisms (Koch phenomenon). Yet others have concluded that the sensitization following tubercular infection lowers resistance to the microorganism.

Soon after the discovery of the tubercle bacillus, Koch made the major mistake of his life by claiming in 1890 that he had produced a material (Koch's Old Tuberculin) which could be used to prevent tuberculosis and also to cure it. Within a few years, these findings were discredited. Others through the years have made claims of having prepared an effective immunizing antigen or vaccine against tuberculosis. These preparations have consisted of killed tubercle bacilli, living attenuated (avirulent) organisms or chemical fractions of the tubercle bacillus. The one vaccine that has received by far the most intensive study and trials in man is the B.C.G. living vaccine of Calmette.

The B.C.G. vaccine is prepared from a bovine culture of the tubercle bacillus first isolated in 1902 and studied for a number of years by Calmette and Guérin. The organism finally lost its virulence for animals and was then studied for its immunizing properties. Although the early immunizing studies of Calmette and Guérin in animals were limited, they and others were convinced that trials in humans should be made. The B.C.G. vaccine (bacilli Calmette-Guérin) was fed to infants in 1922 by Weill-Halle and Turpin. No adverse effects were reported. The indications of an increased resistance to tuberculosis were heralded by Calmette with considerable enthusiasm. Others were more critical of the findings. The children so "immunized" by oral administration did not develop sensitivity to tuberculin but there was more than a little skepticism as to the value of the vaccine in preventing tuberculosis. Soon the peroral 'Calmettization" was given up in all but those areas dominated by French Medicine.

After a lapse of time, interest in the B.C.G. vaccine was renewed particularly by the Scandinavians. They chose to administer the vaccine to tuberculin negative patients by intracutaneous injections. Their results have been much more acceptable in terms of showing a real immunizing

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value for the B.C.G. vaccine. About 5 million patients have been given this vaccine in Norway, Sweden and Denmark and the results carefully followed. Smaller but equally well controlled studies have been made in England using the intracutaneous route of inoculation. Large scale use of the vaccine has been made in recent years under the supervision of the World Health Organization. In all, probably 50 million persons have received the vaccine to date. The overall results of this experience can be discussed with some certainty.

The safety of any vaccine and certainly a living vaccine is of prime concern to the physician. No vaccine is perfectly safe. Post vaccinal complications have been observed in the use of vaccines against small pox, pertussis, rabies, poliomyelitis, et cetera. In the large experience of the Scandinavian physicians, the incidence of progressive tuberculosis due to the B.C.G. antigen is about 1 in one million of those vaccinated, or about one tenth of the incidence of post vaccinial encephalitis observed in New York City several years ago following the wholesale vaccination of about 3 million of the population against small pox. The treatment of the rare case of tuberculosis arising from B.C.G. vaccination is much more satisfactory than that for a central nervous system disease such as post-vaccinal encephalitis.

The degree of protection afforded by B.C.G. vaccination is dependent on several factors, namely: (a) the strain of B.C.G. organism used, (b) the viability of the preparation when used, (c) the technique used in applying the vaccine, (d) the degree of subsequent exposure of the patient and (e) the patient's natural resistance to tuberculosis. Rosenthal[1], in a study made in Chicago, vaccinated new-born children from homes with and without known tuberculous contacts, as well as adults, such as medical students. In the infant group, from tuberculous households, after fifteen years there was a reduction of 75 per cent in morbidity and 89 per cent in mortality in the vaccinated over the nonvaccinated group. In an earlier report by Stein and Aronson[2] reporting on a seventeen-year follow-up involving 2,990 Indians, the morbidity was 4.1 per cent in the vaccinated group and 16.4 per cent in the unvaccinated. The first report of the English Medical Research Council Committee[3] is particularly convincing and instructive. In the group of adolescents vaccinated with B.C.G., the annual incidence of clinical tuberculosis was 0.37 per 1,000. In the unvaccinated control group, the annual incidence of disease was 1.94 per 1,000. The few cases of tuberculous meningitis and miliary tuberculosis diagnosed were all in the unvaccinated group. Similar findings from the Scandinavian countries, support the value of B.C.G. in reducing the morbidity and particularly the mortality from tuberculosis.

A third consideration of concern to the physician is the fact that following B.C.G. vaccination, the patient reacts to tuberculin. The conversion to a positive reaction persisted for four years in 92 per cent of one group vaccinated as infants by Rosenthal. In general, it may be stated that adults receiving this vaccine will remain tuberculin positive for one and one-half to two years. This induced conversion may complicate the diagnostic problem of the physician in detecting early cases of the disease. Public Health Officials in this country give considerable weight to this aspect of B.C.G. immunization. However, in patients vaccinated by the multiple puncture technique, about fifty times as much tuberculin (250 T.U.) is required to elicit a reaction as would be the case in early tuberculous disease.

Investigations are proceeding in various laboratories to develop immunizing agents that may be superior to the B.C.G. vaccine in one or all of the following respects: (a) a non living vaccine, (b) one that will create a greater resistance to the disease in the patient and (c) one that will not sensitize the patient to tuberculin.

The advent of the "wonder" drugs brought high hopes to those concerned with the treatment of infectious diseases. Unfortunately, the microbes held an ace card that was not anticipated, namely, their ability to mutate and give rise to drug resistant forms. This has become a particularly serious problem with the staphylococci. At present, chemotherapy is losing ground to the staphylococci and the problem has become very serious. There is no reason to doubt that trouble of the same sort is going to confront the medical profession in the treatment of tuberculosis. Even as the disease is now treated, it is estimated that in 1976 there will be 36,000 new cases in the United States and a continuing load of 180,000 active cases to be treated. Hence, the need for developing a satisfactory vaccine for the prevention of this disease.

In reviewing briefly some of the current efforts to develop a more satisfactory vaccine for the prevention of tuberculosis, it may be helpful to restate certain facts and ideas that guided the author in setting up a program to develop a better immunizing antigen about twelve years ago. These were published in 1953.[4]

1. Virulent bacteria differ antigenically from avirulent organisms and therefore, should be used as the starting material in preparing a vaccine. (B.C.G. is essentially avirulent and of bovine, not human origin.)

2. The chemical substance or complex associated with virulence, the "virulence factor," must be preserved with a minimal change in chemical structure and must be present in the immunizing antigen.

3. There may be present in the organism, as it grows in the patient or *in vitro*, a factor which interferes with the immunizing or resistance mechanisms of the host.

4. The "virulence factor," probably present in the less virulent B.C.G. only to a limited degree, would be most effective as an immunizing antigen if freed of the "resistance-lowering" or "immunity-poisoning factor," if such exists.

Killed suspensions of tubercle bacilli have received limited attention as immunizing agents by many investigators. The order of immunity developed has never been impressive probably because of the large challenge dose used to demonstrate immunity and possibly because of the effect of heat or strong chemicals on the "immunizing antigen."

During the past ten years, Sarber et al.[5] have developed procedures for killing virulent strains of the human tubercle bacillus by ultraviolet irradiation. Vaccines so prepared to have been found to have an immunizing effect on guinea pigs equal to that of several B.C.G. preparations used as controls as shown by challenge with virulent tubercle bacilli. This type of preparation has been recently used[6] in 100 infants in South America. No unfavorable reactions were reported. Dubos et al.[7] have more recently shown some value for killed tubecle bacilli as immunizing agents. There can be little question that some increased resistance to tuberculosis is developed in animals injected with killed tubercle bacilli. This order of immunity may approach or be equal to that developed by B.C.G. Such vaccines are nonliving and have the marked advantages of being more stable on storage and less subject to subtle mutations of the parent strain with resulting changes in immunizing properties. The very slight danger (one in a million) of developing progressive tuberculosis as the result of immunization with B.C.G. is also removed. Sensitization of the patient will develop as with B.C.G. To date, adequate trials in man have not been made with the killed vaccines.

The ultimate aim of the modern immunologists is to isolate the "virulence factor" of pathogens with the hope of using this chemical fraction as an immunizing agent. The injection of such a purified antigen or "vaccine" into a patient does not subject him to trauma from the non-immunizing componets of the microorganisms. These componets may result in undesirable local reactions, sensitization or interference with the functioning of the immunity mechanisms of the host. The latter effect has been one that the author and his colleagues have sought during the past decade but with only inconclusive results. If such an effect is demonstrated, it might aid materially in explaining the poor immunological response of the patient to his own disease in contrast to the patient with pneumococcus pneumonia. Dubos and his colleagues, in work yet unpublished, have obtained evidence of an adverse effect of certain components of the tubercle bacillus on the defense mechanisms of the host.

Fractions of the tubercle bacillus have been examined in recent years for their immunizing properties. Choucroun,[8] Kropp and Foley,[9] Raffel,[10] Negri,[11] Smith, Grover and Nungester,[4] and Weiss and Dubos[12] have all reported that such fractions have immunizing properties. This approach holds much promise for the future. The results to date in animal studies indicate that certain of the fractions of the tubercle bacillus may immunize but not sensitize to tuberculin. If fractions could be obtained which had somewhat greater immunizing properties than those so far isolated, a highly practical vaccine would be available; one that was free of living organisms, and would not sensitize to tuberculin. Some of the substances, (polysaccharide complexes) so far studied have immunizing properties approaching those of B.C.G.

The tubercle bacillus is a rather complex chemi-

cal system in terms of its structure. From the early classical studies of Anderson and his colleagues, we know something of its complex chemistry. However, since the time of his investigations, two new chemical tools, column chromography and infra red spectrophotometry have been used by Smith, Randall and their colleagues,[13] in unraveling the finer chemical structure of various types and strains of the tubercle bacillus. In this work, continuing attention is given to the immunizing properties of the various fractions which they isolate. This co-operate work, first started when Dr. Smith was in the Department of Bacteriology at the University of Michigan, has continued, with the biological work being done by Dr. Smith at the University of Wisconsin. Some of the chemical and the physical studies are being supervised by Dr. Harrison Randall, Professor Emeritus of Physics at the University of Michigan. It is hoped that this work will contribute to the development of a non-living but effective immunization antigen.

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MORE MEDICAL STUDENTS TO START AT WAYNE

With legislative approval, Wayne State University's Board of Governors has voted to increase the College of Medicine enrollment from 75 to 125 freshmen students, beginning in September, 1958.

Funds to cover expansion will come from the State's general appropriation to the University of $9,718,900. Estimated cost for the additional students is $285,000 for the first year.

By 1962, the total medical school enrollment is expected to be 500 as compared to the present 300.

The University's action climaxed a concerted two-year effort by a group of lawmakers and health officials to head off a growing shortage of doctors in Michigan.

From the beginning, all proposals indicated that expansion of Wayne's College of Medicine could be done practically and economically. This was substantiated by a special report to a legislative study committee on higher education by Dr. William T. Sanger, chancellor of the Medical College of Virginia.

The Sanger report said that Wayne's medical school should be expanded to accommodate 200 entering students a year before consideration is given to a third medical school in Michigan.

Some Developments in Relation to Pertussis Vaccination

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THE decline in death rates due to pertussis during the past decade has been of such magnitude that to explain it we need to identify some specific factors over and above those responsible for the general downward trend observed during the past fifty years. Whatever other contributory factors there may be, such as improved living conditions and better medical care, the sharp decline in mortality rates has accompanied a progressively wider application of immunization procedures demonstrated to be effective in controlled field trials. This is illustrated by the figures for cases and deaths due to whooping cough in Grand Rapids and Michigan, as noted recently by Eldering.[1] Deaths in Michigan from 1932-1956, by five-year periods numbered respectively, 732, 474, 286, 143, and 50; for the single years 1956 and 1957, there were seven deaths each. In Grand Rapids, for the same five-year periods, deaths numbered 10, 5, 4, none and none; and for the years 1956 1957, none. Eldering called attention to the percentagewise shift in the age group affected by whooping cough. In answering the question whether there has been a postponement of cases, age specific morbidity rates are needed. In the accompanying chart (Fig. 1), the data from 1928-1953 are charted as five-year moving means, by age group.

There has been a decline in the rate for all age groups under ten years; this decrease is greatest from ages one to four years, and thus produces a shift in the proportional (or percentage) age distribution. The morbidity rates in the age group over ten years are too low to present on this graph, but have shown no significant increase or decrease. In relation to the graph, it should be recalled that the early field studies in Grand Rapids and Kent County by Kendrick and Eldering[2] were reported in 1939; relatively widespread use of pertussis immunization in the community was achieved during the early 1940's.

Even against the encouraging background of demonstrated protective vaccination, and currently declining mortality, we cannot afford to forget that in the United States whooping cough

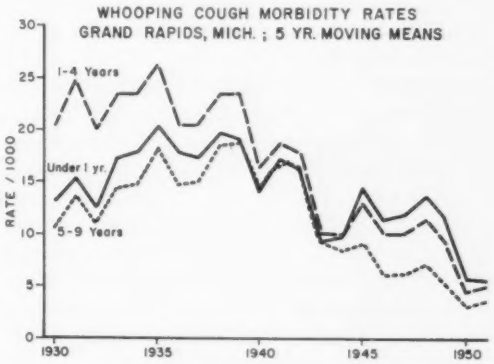

Fig. 1.

is still high on the list of communicable diseases of children from birth to fourteen years. For the period 1940 to 1948, it is pointed out by Gordon and Hood[3] that whooping cough killed almost three times as many infants under one year of age as measles, mumps, chicken pox, rubella, scarlet fever, diphtheria, poliomyelitis and meningitis all together; also the effect of the disease on the health, growth and resistance of children can be very damaging; and it is responsible for more lost school days per case than any other acute disease. Whooping cough therefore is not a disease to be considered lightly; and problems of immunization need continuing consideration. In 1944, Felton and Willard[4] made a comprehensive historical review of pertussis vaccination and discussed the current status; at the same time the Council of the American Medical Association accepted certain designated types of vaccine. Since then the situation has changed in a number of important respects. Convincing support of the efficacy of *Bordetella** *pertussis* vaccines was added to the

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**Bordetella pertussis* is now the accepted designation, replacing *Haemophilus pertussis.*

accumulating evidence, by the results of the well-designed, controlled field trials in England reported by the Medical Research Council[5] in 1951. Their findings clearly demonstrated that under the same experimental conditions pertussis vaccines could differ widely in their protective properties. In comparison with the other vaccines tested, two lots prepared by the Michigan Department of Health Laboratories and used for reference, gave a considerably greater degree of protection. The Michigan vaccine had been prepared according to the methods used successfully in the Grand Rapids studies. Subsequently, vaccines prepared in England by similar procedures were also highly protective.

In 1952, a conference was organized by the World Health Organization for critical consideration of diphtheria and pertussis immunization.[6] The main emphasis was on techniques of production and evaluation of immunizing agents. The conference recognized particularly the difficulties involved in defining methods of preparing pertussis vaccine that would ensure consistently good results, and pointed out the essential need for reliable potency tests; they considered that the intracerebral mouse-protection test offered promise, and that a vaccine which gave poor results in this test should not be issued for use. The work of the conference provided an impetus to efforts toward standardization.

Laboratory Potency Tests and Their Application

When the Council of the American Medical Association accepted pertussis vaccines[4] in 1944, they specified "prepared according to the method of Sauer or of Kendrick and Eldering or of Harrison and Bell." At that time there was no accepted potency test for a particular lot of vaccine; the best that could be done was to prepare a vaccine as nearly as possible like one that had provided specific protection of children in controlled field trials. Any improvements in method, any progress towards better vaccines and procedures for immunization, were dependent on the development of laboratory methods for evaluating efficacy. A field trial to study such suggested change, no matter how promising, was obviously out of the question. With the development of the intracerebral mouse protection test[7] it became possible to use potency as a basis for the release of each manufactured lot of vaccine; since 1948, after a trial period of approximately two years, all pertussis vaccines released for distribution by manufacturing laboratories in the U.S.A. have been required by the National Institutes of Health to pass a mouse protection test in comparison with a reference vaccine. Subsequently, a reference pertussis vaccine was designated by Great Britain; more recently, acceptance of an international standard based on comparative tests in laboratories of different countries, was an important step towards the improvement and standardization of pertussis vaccines on a world wide basis. In the Minimum Requirements of the National Institutes of Health for pertussis vaccines, potency now is expressed in terms of mouse protective units, rather than bacterial concentration; this latter being specified only as an upper limit, to avoid unnecessarily high content of foreign protein.

Mouse protection tests have provided a laboratory basis for evaluation of experimental procedures and modified types of vaccine. In the controlled field trials reported in 1956 by the Medical Research Council of Great Britain[8] the results were summarized for two series of controlled field trials in which fourteen pertussis vaccines were tested for their protective potency in 28,799 children and substantial protection demonstrated. One of the antigens had been prepared from cultures grown in Cohen-Wheeler's blood-free medium and had been shown to protect mice in laboratory potency tests. In this first controlled trial of such a vaccine, the protection of children was of the same order as with vaccines prepared from suspensions of culture cultivated on Bordet-Gengou medium; one of them, a reference Michigan vaccine. Of particular interest in this report was the comparison of eighteen vaccines, including several that had given varying results in earlier trials, for their efficacy in children and their potency in mouse protection tests. The positive correlation between field trial and laboratory results promotes confidence in accepting mouse protection as an indicator of probable efficacy of pertussis vaccines for human use.

Antigens Separated from Cultures of B. Pertussis

During the past decade or more, important investigations have been concerned with attempts to isolate the essential or protective component of pertussis cultures, thus eliminating what may be unneeded portions of the whole culture, and perhaps reducing non-specific local or systemic reactions. The "protective antigen" or PA of Pillemer[9]

and the non-cellular antigen described by Felton and Verwey[10] are examples. Both of these products protect mice against intracerebral infection with *B. pertussis,* and may be expected to protect children against pertussis if the practical problems concerned with their manufacture, administration and evaluation can be solved satisfactorily. Pillemer's antigen is under study in England, and preliminary results mentioned in a recent paper by Cockburn[11] suggest that it protects children as well as whole-culture antigens with which it is being compared. Although the Pillemer antigen had given good results in mouse protection tests, there was very little stimulation of agglutinins in mice, suggesting that the agglutinin-stimulating component may not be essential to protection. This experience illustrates the unforeseen problems that may arise from any change in the type of vaccine. With the whole-culture vaccine, agglutinin may well serve as an indicator of protective response whether or not the agglutinin itself is protective. If, however, it proves possible to isolate a protective antigen entirely free of agglutinin-stimulating substance for use as vaccine, it is apparent that a different indicator of protective response in the vaccinated child would be needed.

In a current trial of their non-cellular antigen, Felton and Verwey[10] have made a progress report on 197 injected children in comparison with a similar group injected with whole-culture vaccine and a non-immunized control group accumulated from the population. They found evidence of a satisfactory level of immunity and believed that the local and systemic reactions following injections of the non-cellular antigen were milder than following whole culture vaccine.

Use of Combined Multiple Antigens

Without question, most pertussis vaccine in use today in the United States is combined with diphtheria and tetanus toxoids (DPT). The question has arisen most naturally as to the effectiveness and practicability of other combinations. In particular, with the demonstration of the effectiveness of poliomyelitis vaccine by the evaluation study directed by Francis,[12] current interest has been directed towards the possibility of combining polio vaccine with DPT. For several years this problem has concerned the Committee on Multiple Antigens of the American Public Health Association. Preliminary experiments in animals by Kendrick and Brown,[13] together with continuing unpublished experiments, have uncovered no contraindications to the use of such a combination of antigens; and have demonstrated serological responses to the individual components.

A discussion of combined multiple antigens requires a consideration of the possibility of one antigen interfering with or "crowding out" the immune response to another in the mixture. The clearest demonstration of this phenomenon was made by Barr and Llewellyn-Jones[14]; when guinea pigs already immune to diphtheria were immunized with combined diphtheria and tetanus toxoids, the response to diphtheria was excellent but to tetanus, lower than in guinea pigs not immune to diphtheria. The relation of this "crowding out" effect to practical problems of specific immunization in humans is not now clear. That it may occur under certain particular conditions is suggested by Chen et al,[15] who observed a weaker response to the pertussis and tetanus components of DPT in the latently diphtheria-immune group than in the non-immune. Perhaps it should be pointed out that these investigators measured the pertussis response only on the basis of circulating agglutinin, not on protection.

An interesting effect of pertussis vaccine when mixed with diphtheria and tetanus toxoids is the enhancement of their potency; that is, pertussis vaccine behaves as an adjuvant. A mixture of plain diphtheria toxoid and pertussis vaccine has a potency comparable to the same toxoid, alum precipitated, or adsorbed to a mineral carrier; however, alum precipitated toxoid, in which the potency already has been increased, does not appear to be enhanced further by mixing with vaccine. As to any possible enhancement of the potency of viral antigens by mixing with pertussis vaccine, experimental data are at present insufficient to provide an answer; the advantage of such an effect if present is obvious.

If we attempt to take into consideration all available data on combined antigens, what appears to stand out is the accumulating evidence of successful experience in the use of such products. The advantages are so great that much effort can be afforded in studying their applications and defining their limitations. Should further research uncover certain problems, for example, if interference should be recognized as a real limitation under particular conditions, we may be confident that the experimental approach also will provide

an answer. For further discussions of the use of combined multiple antigens, and some of the implications, reference may be made, among others, to papers by Cockburn,[16] Sauer,[17] and Volk, Top and Bunney.[18]

Current Procedures for Immunization

An expression of the current opinion of practicing physicians and investigators on immunization procedures is to be found in the 1957 Report of the Committee on The Control of Infectious Diseases of the American Academy of Pediatrics.[19] The warning to read the instructions that accompany the product of any particular manufacturer is emphasized. These will make clear the volume and number of injections to contain the required number of mouse protective units per total human dose. It is important to keep in mind that dosage schedules are not static. Related perhaps to a change in the immunizing agent, perhaps in the light of newly discovered knowledge of individual immunity response, or perhaps on the basis of demonstrated changes in the immunity status of the community, modifications of procedure may be indicated. As one example of such a revision we need only recall the change from the early use of a one week interval between injections to the present longer interval of four weeks or more as dictated by experimental results.

It can be hoped that continued study will give a sounder basis for selection of the time and size of dose for the recall or "booster" injection. There is considerable evidence from laboratory data that after an adequate primary immunization, waning immunity can be recalled with a very small injection of specific antigen. In the early study of Kendrick, Eldering and Thompson[20] on a reinforcing or "booster" injection in kindergartners who had received their primary course from one to four years previously, a dose estimated as 5 billion bacteria stimulated a marked opsonic response. The presently recommended dose is roughly four times the dose used in that study. Further studies are needed to determine whether a smaller recall dose might be adequate under present conditions of usage.

The question of how early to start immunization is one that has received much discussion and has been the subject of a number of investigations. According to the answer to this question, procedure will be modified. For example, the time for a booster injection will depend on when the primary immunization was given. Di Sant'Agnese[21] has reviewed the findings of several authors on the capacity of new born infants to produce antibodies, and has presented his own data in this and other papers. He urges that, pending further work, a conservative approach be made to the question of immunization of infants less than three months of age. The argument that infants should be immunized immediately after birth because of the relatively high mortality in the very young infant may not be as telling as it might at first appear. While the case fatality rate during the first few months is high, the incidence is low; and mortality may be reduced indirectly by preventing the disease in the older children where the incidence is high, thus reducing exposure of the young infants. Of course, the decision as to the age at which infants should be immunized must be based on a number of practical as well as immunological considerations. For example, there is the problem of integrating protective measures against several diseases when combined multiple antigens are used. While further information and experience are accumulating, nothing will be lost by the conservative approach suggested by Di Sant'Agnese. For the very young non-vaccinated infant known to be exposed in his household, specific antiserum is available. This is the place for the use of hyperimmune serum—in the exposed infant, in the early stage of incubation; under these conditions the disease may actually be prevented.

In the event that a child has missed primary immunization in infancy as recommended, there is no experimental basis for concern over vaccinating the older child if circumstances indicate it should be done. In the preliminary study of pertussis vaccine in Grand Rapids, children of five and six years were given a primary course, and for many years booster injections were given to kindergartners who had not received them within the previous year. Of course, as with other bacterial antigens, somewhat more marked reactions may be expected with increasing age. Even so, in adults under immunization for production of hyperimmune antiserum, no unusual difficulty has been encountered.

Reactions to Vaccine Injections

Local and systemic reactions to pertussis vaccine alone and combined with toxoids have been studied by many investigators. The questions

raised by Byers and Moll,[22] among others, concerning the possible correlation between injections of pertussis vaccine and subsequent encephalopathies, and then the question of the possible provoking-effect of injections of vaccine in poliomyelitis or localization of paralysis, have been discussed by various authors. In the Medical Research Council study,[8] reactions were observed in over 10,000 visits and it was concluded that local and general reactions were not serious. Looking for possible instances of encephalopathies, they observed that among over 30,000 vaccinated children 34 had their first recorded convulsion 4 to twenty-eight days after injection, however, they found no reason to consider that the convulsions were precipitated by the injections. In these trials it is their policy to accept for injection only well children and not within a month after attacks of measles, mumps, influenza, chickenpox and similar diseases or smallpox vaccination. They do not accept children with a personal or family history of convulsions, epilepsy, hydrocephalus or mental defect. In children with such histories, the private physician must weigh the possible though rare ill effects of vaccine injections against the likelihood of occurrence of whooping cough and its attendant dangers in the individual children concerned; and he will take into consideration that while the occurrence is rare, encephalopathy occurs more frequently in association with the disease whooping cough than in association with the vaccination procedure. As to possible effects of vaccine injections in provoking poliomyelitis or localizing paralysis, such occurrences at most must be rare indeed; with more extended protection against poliomyelitis they can be expected to be still rarer. The statement of the conference on this problem called in 1952 by the United States Public Health Service[23] was included in the report by the conference of the World Health Organization,[6] and its acceptance is implied in the current recommendations of the Academy of Pediatrics.[19]

In summary, the importance of whooping cough is such that specific immunization must be maintained. Research is needed as a basis for improving the immunizing agents and methods of administration. Evaluation is needed of the effect that a program of immunization has on the immune status of the individual and of the community. Recognition of the changing status is a prerequisite to intelligent modification of immunization procedures in the effort to obtain the best possible results in terms of specific protection.

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Current Investigations of Immunization Against Poliomyelitis

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THE nationwide field trial of inactivated trivalent poliomyelitis vaccine in 1954 proved conclusively that this method of immunization against the disease was effective and practical.[1,2,3] Advances and improvement in the manufacture of the vaccine have resulted in increasingly consistent preparations both as to antigenicity and safety.[4,5,6] The poliomyelitis surveillance program of the U. S. Public Health Service has accumulated a vast amount of information proving that the vaccine has resulted in a sharp reduction in paralytic poliomyelitis wherever tested. In 1955, data from approximately twenty states show that the incidence of paralytic poliomyelitis was from two to more than five times as great in unvaccinated children as in those receiving vaccine.[7] There was a less marked but favorable difference reported for the nonparalytic cases. In 1956, the over-all effectiveness of the vaccine in preventing paralytic poliomyelitis was about 75 per cent in spite of the fact that a large proportion of the vaccinated population had received less than three doses.[8] Furthermore, specimens from many cases reported as poliomyelitis, especially nonparalytic cases, have been subjected to laboratory examination with the result that poliomyelitis was ruled out either by failure to isolate the agent or by the actual isolation of other causative organisms. As an example, stool specimens from 458 cases diagnosed clinically in Michigan during 1957 have been processed in the Virus Laboratory of the School of Public Health and poliomyelitis was confirmed in only thirty-nine. Thirty-two of these isolations occurred in the unvaccinated group of 203 individuals. In contrast, the remaining seven isolations were made from a total of 255 subjects who had received one or more doses of vaccine. Thus a ratio of almost six to one in favor of the vaccine was demonstrated. This extensive laboratory investigation of diagnosed cases has brought to light an increasing number of other viral agents such as Coxsackie and Enteric Cytopathogenic Human Orphan (ECHO) viruses and their significance in clinical disease is rapidly becoming more apparent. They are commonly involved in outbreaks of aseptic meningitis and other illnesses closely resembling non-paralytic poliomyelitis.

Thus the widespread use of the Salk vaccine since its inception has provided overwhelming evidence of its effectiveness and its use is recommended without reservation. An interesting corollary of vaccination with inactivated virus is that individuals so immunized may still be infected subclinically upon subsequent natural exposure with the result that their immunity is greatly reinforced while being protected against the paralytic disease at the same time.

Recent Studies on Administration of Vaccine

The field trial of 1954 was conducted in early school age children and a set schedule of three primary inoculations within a five-week period had been rigidly adhered to. Many questions, therefore, were immediately apparent. Was the dosage schedule designed to elicit optimal response in vaccinated subjects or could it be improved? Would secondary immunization give a booster effect and what would be the best time for its administration? Would the vaccine be as effective in infants and preschool children? Do inoculations of gamma globulin interfere with active immunization? What effect upon the response would occur following a marked delay between the first and second injections of vaccine? And perhaps most importantly, what is the duration of immunity following vaccination? Additional studies to answer these questions, therefore, were designed and some of them were actually begun while the field trial was in progress. As a result the recommended dosage schedule was changed to the use of two primary injections several weeks apart followed by a secondary or booster inoculation six to seven months later.[4] The im-

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portance of this booster injection in completing the immunization schedule has been repeatedly confirmed[4,9-13] and all the available evidence points dramatically to the fact that this inoculation is the greatest single factor insuring an adequate immune response. It has been found that preschool children do respond well to the vaccine and that infants as young as two to three months of age also develop satisfactory antibody levels.[14] No untoward reactions have been observed even in this youngest age group. These facts have enabled pediatricians to inaugurate immunization very early in life and therefore decrease the incidence of disease in this extremly susceptible age group. Another study has demonstrated that the administration of twice the usual dosage of gamma globulin just three days prior to the injection of poliomyelitis vaccine does not interfere in any way with the response to active immunization.[11] An investigation of over 200 school children in whom the second injection of vaccine was delayed five to six months showed that this delay does not invalidate a satisfactory response but in fact may improve it.[15]

Another type of study which is being conducted at present concerns the administration of multiple antigen preparations containing the toxoids of diphtheria and tetanus, pertussis antigen and the three types of poliomyelitis virus. The results of preliminary experiments in animals with such a vaccine have been published.[16] Several other experimental preparations are under study and the results in animals are encouraging in that satisfactory antibody responses to the individual components of the multiple antigen are obtained. These vaccines will be tested in infants in the near future and if proved efficient will greatly simplify the process of immunization against four diseases of childhood simultaneously.

Duration of Immunity

The aforementioned studies, although time consuming, were relatively short term projects. But the important question of duration of immunity following vaccination with killed virus preparations was by definition one that required a long time to answer. In fact, the longer the interval since vaccination the more significant would be the information obtained. Data on this subject are being accumulated in several ways. In one study, two groups of school age children in different counties of Michigan who had received their primary vaccination during the field trial of 1954 and their secondary immunization one year later in 1955 have been studied throughout this period with the latest serological examination in 1957. In addition, a group of preschool children and infants who had received their inoculations at approximately the same time have been studied in the same manner.[17] The results show that regardless of the extent of primary response a marked antibody rise followed the secondary or booster stimulus given six months to one year later and that even two years after the secondary stimulus the serum antibody levels remained remarkably high. In fact, the decline of the mean post-booster antibody level of 461 to a level of 102 in vaccinated school children during the two year period is almost identical numerically with levels of 512 and 122 reported by Lennette in patients convalescent from paralytic disease which had been confirmed by virus isolation.[18] Properly scheduled vaccine can, therefore, be expected to give good titers which are sustained for at least two years.

Another study designed to reveal the present status of sero-immunity in children vaccinated under field conditions is being conducted at present. Through information contained in the files of the Vaccine Evaluation Center it was possible to select a representative number of children who had participated in the field trial of 1954 and who had been found to be serologically negative to all three types of poliomyelitis before receiving their inoculations. These names were compiled into separate lists and health officers in the various counties of Michigan and New York were asked to co-operate in the study by obtaining specimens of blood during the period of late 1957 and early 1958. In addition, a history of contact with known cases of poliomyelitis and a record of vaccine injections since the field trial were requested. Through the co-operation of these health officers many such specimens have been obtained and tested in the University of Michigan Virus Laboratory.[19] The results on approximately 200 of these specimens have been analyzed by correlating the present serum antibody levels with the history of vaccination and prove very interesting. Although there was a great variation in vaccination histories since the field trial, by far most of the children were found to fall into one of four groups: (1) those vaccinated three times in 1954 and

once in 1955, (2) those receiving placebo three times in 1954 and two injections of vaccine in 1955, (3) placebo in 1954, two injections of vaccine in 1955 with a third in 1956, and (4) placebo in 1954, two injections of vaccine in 1955 and a third in 1957. The geometric mean antibody levels are presented in Table I where it can be seen that the highest titers at the present time are found in the original placebo group which had received their last of three injections only a year ago in 1957. However, the levels in those not receiving any vaccine during the three years since 1955 are indeed significant especially in those who had only two injections. In fact, a small number of children who had received vaccine three times in 1954 and nothing during the four years since that time showed levels of ten, thirty-two and fourteen to the three types respectively, a remarkable record for the persistence of antibody.

TABLE I.

SEROLOGIC STATUS OF CHILDREN NEGATIVE TO THREE TYPES OF POLIOMYELITIS

History of Inoculation				Mean Antibody Titer—1958		
				Type		
1954	1955	1956	1957	I	II	III
Vaccine 3x	—	—	—	10	32	14
Vaccine 3x	Vacc. 1x	—	—	24	51	12
Placebo 3x	Vacc. 2x	—	—	11	22	5
Placebo 3x	Vacc. 2x	Vacc. 1x	—	32	64	19
Placebo 3x	Vacc. 2x	—	Vacc. 1x	64	218	24

There is little doubt that when all the results are tabulated the vaccine will again be shown to be highly effective in stimulating persisting sero-immunity.

A third study of immunity to poliomyelitis concerns the response of pregnant women to vaccination and the duration of passively transferred materal antibodies in the infant.[20] Vaccination was performed during the seventh and eighth months of pregnancy. Serum specimens were obtained from the mother before vaccination, at delivery, from cord blood, and from the infant at twenty-four hours, one week, one month, two months and three months after birth. The results of serum antibody titrations on these specimens show that the mothers responded to vaccination with elevated antibody levels and that the response of those with some antibodies before vaccination was greater than in those without. Statistical analysis of the serum titers of mothers at delivery, that of the cord blood, and of the infant at twenty-four hours showed that the poliomyelitis antibody content of the three specimens was essentially the same indicating that the infant also profits serologically from vaccination of the parent. The titers of passively transferred antibodies in the infants declined with age at the same rate regardless of whether they had been stimulated naturally with infection or artificially with vaccine. Many infants had demonstrable antibodies at the third month of life but the duration of antibody was a direct function of the height of the antibody titer in the mother at the time of delivery thus demonstrating the value of vaccination in heightening antibody levels of pregnant women and their offspring and indicating the probable protective influence in a period of increased risk.

Live Virus Vaccine

During the last six years considerable work has been conducted on the safety and efficacy of orally administered attenuated but live virus vaccines.[21-23] The underlying concept of these studies has been the deliberate establishment of a subclinical infection in the alimentary tract in the hopes that the subsequent immunity would be long lasting. Serum antibodies have, in fact, been demonstrated as long as six years after feeding virus in a small group of children. However, the critical problem which needs to be proven beyond a shadow of a doubt if these viruses are ever to be widely disseminated is whether such attenuated viruses are capable of reverting to their original virulent state following passage through human beings. Resistance in subjects fed attenuated virus is demonstrated by the much more limited period of alimentary infection after refeeding than is seen in individuals who have previously been vaccinated with inactivated viruses but some reversion to an increased state of

neurotropism for monkeys has been detected after one human passage. Furthermore, it would appear that attenuated viruses of the three types must be fed separately in order to avoid interference with their multiplication by the most dominant type. One interesting possibility is currently being investigated, namely, the administration of two or more injections of killed virus vaccine followed by the feeding of live virus.[24,25] This procedure would in effect supply the added stimulus of actual subclinical infection with subsequent prolonged immunity to individuals who were protected against the paralytic disease but still capable of excreting virus for several weeks following re-exposure. Another possibility, although not likely in this country where millions of children have already been immunized with Salk vaccine, is a careful large scale field trial similar to that of 1954 in children with live attenuated virus vaccines to test its actual effectiveness and practicability.

Summary

The highly successful field trial of Salk poliomyelitis vaccine in 1954 has been followed by additional and overwhelming evidence of its ability to sharply reduce the incidence of paralytic disease. This vaccine has now been found to be effective and safe in all age groups including very young infants and most important, significant sero-immunity has been demonstrated to persist for as long as three to four years. Thus, current investigations on immunization against poliomyelitis are not concerned with confirmatory evidence of its proven value but in attempting to find ways that it may be even more useful in eliminating this disease.

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Vaccination against Respiratory Diseases Caused by Viruses

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INFLUENZA as commonly encountered has been caused by either Type A or Type B influenza virus which are immunologically distinct agents, although the diseases they produce are otherwise closely similar. Epidemics recur at intervals of a few years associated with slight antigenic modification in the prevalent strains of the virus. At certain times the shift in character of strains is of a major nature. Major antigenic shifting appears to occur every ten to fifteen years.

The results of a series of studies carried out since 1942 by the Commission on Influenza of the Armed Forces Epidemiological Board have largely served to establish the effectiveness of influenza virus vaccines. The findings are summarized in Table I. Protective effect is expressed as the ratio of attack rate in controls to that in vaccinated subjects. During the influenza A epidemic of 1943, at least 3.6 times as many cases occurred among unvaccinated persons as among vaccinated persons. In 1945, a higher degree of protection against influenza B was shown. However, in 1947, the A-prime strains unexpectedly appeared; they differed distinctly from the strains representative of earlier years of which the vaccine was made. That vaccine did not effectively stimulate antibody against the A-prime strains. Nevertheless, it was thus firmly established that strain differences among influenza viruses, measured serologically, can be of importance with respect to immunization of man. The problem was met by putting A-prime strains in all subsequent vaccines, and the record shows that between 1950 and the Spring of 1957, an important degree of protection against influenza A-prime was uniformly produced by vaccination even though differences in strains were seen in various years.

Antigenic variation among strains of influenza B has been a less prominent feature, yet the results of the trials of 1955 with Lee strain (1940) showed that here, too, the time had come to update vaccines by adding a more recent isolate. Subsequent vaccines have contained the Great Lakes strain of influenza B isolated in 1954.

Concern in this country with Asian influenza began when in May, 1957, Dr. Maurice Hilleman, at that time Chief, Department of Respiratory Diseases, Walter Reed Army Institute of Research and also an Associate Member of the Commission on Influenza, reported by telephone to the Commission that the epidemics of influenza then occurring among civilians in Hong Kong and among the military in the Far East were caused by strains belonging to a new antigenic family of influenza A viruses. A series of steps was taken by the Commission to evaluate the significance of his findings. Hilleman had observed that antibody against the new strains—now called Asian—was not readily demonstrable in the serums of adult Americans and that little or no antibody increase was found with these strains in cases of influenza A-prime observed in Americans in early 1957.[1] These observations were promptly confirmed and extended in the laboratory at Ann Arbor. There it was shown that antibody increase to the Asian strains then available could not be demonstrated after vaccination with potent polyvalent vaccine containing Swine, A, and A-prime viruses. Nor could the new strains be typed by hemagglutination-inhibition (HI) tests with serums of ferrets convalescent from infection with prototype strains isolated in former years.

Profiting by the experiences of 1947 and of 1955, rapid action was taken to obtain influenza virus vaccines containing an Asian strain. Early, the Commission on Influenza began to evaluate the protective effect of the vaccines that could be produced at that time. The first formulas were empirically derived yet they proved to be reasonably satisfactory. In the meantime, the national health agencies and the biological manufacturers

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Certain of the investigations reported were conducted under the auspices of the Commission on Influenza, Armed Forces Epidemiological Board, Office of the Surgeon General, U. S. Army, Washington, D. C.

TABLE I. SUMMARY OF RESULTS OF VACCINE TRIALS CONDUCTED BY THE COMMISSION ON INFLUENZA

Year	Prevailing Type	Concentration of Vaccine	Number Vaccinated	Number Cases	Rate	Number Controls	Number Cases	Rate	Protection Ratio
1943	A	5000 HU	5806	114	1.96	5776	408	7.06	3.6
1945	B	5000 HU	1150	10	0.87	2150	241	11.21	12.9
1947	A—prime	5120 HU	10328	743	7.19	7613	616	8.0	1.1
1950	A—prime	300 CCA	670	8	1.2	2082	78	3.7	3.1
1951	A—prime	500 CCA	2596	13	0.5	5228	105	2.01	4.0
1952	B	700 CCA	207	15	7.24	430	83	19.32	2.7
1953	A—prime	750 CCA	5994	57	0.95	5527	316	5.7	6.0 CR8.1*
1953	A—prime	750 CCA	2616	16	0.61	4865	135	2.77	4.5
1955	B	50 CCA Adj	2000	43	2.2	2000	70	3.5	1.6 CR2.2*
1957	A—prime	750 CCA	1188	11	0.92	1216	62	5.1	5.5
1957	Asian	250 CCA Mono	916	20	2.18	1448	55	3.79	1.7
1957	Asian	200 CCA Mono	775	46	5.93	806	121	15.01	2.5
1957	Asian	400 CCA Mono	649	12	1.73	1238	65	5.25	3.0
		400 CCA Poly	564	9					
1957	Asian	200 CCA Mono	1869	62	3.32	1665	126	7.61	2.3
		750 CCA Mono	1665	29	1.74				4.4
1957	Asian	200 CCA Mono	1080	43	3.98	1444	234	16.2	4.1

*CR—Corrected ratio.

moved effectively to produce more than 50 million doses in 1957. The last five entries in Table I show the results of a clinical appraisal of the efficacy of vaccination in controlled studies during the recent pandemic of Asian influenza. These findings have already been published in detail.[2] The effectiveness of vaccines was studied by four groups of investigators in a comparison of 12,002 test subjects who received certain monovalent or polyvalent vaccines with 9,363 contratest subjects who received placebo injections. The estimates of effectiveness, based on relative respiratory illness rates, ranged from 42 to 67 per cent in the various groups. The trends are sufficiently distinct to indicate the final effects which may even be increased when laboratory studies identify and eliminate cases of respiratory disease caused by agents other than the Asian virus. An important degree of protection was observed in all the studies and the amount of protection was enhanced at higher doses of vaccine. The studies indicate that doses of 200 CCA units given subcutaneously were less than optimal, and that vaccines at 400 CCA units or above gave higher and more uniform protection. For example, at Fort Ord, (Table I, 11th entry) using the early vaccine of 200 CCA potency, an effect of 45 per cent was obtained, while in the later study with 400 units (Table I, 13th entry), an effect of about 70 per cent protection was obtained with a single dose. This information played a paramount role in guiding the decision to increase the potency of Asian virus vaccines. Clearly, the fruits of continued investigation and of constant vigilance again firmly demonstrated that vaccination is an effective method of protection against epidemic influenza when proper vaccines are employed.

Indications for Vaccination

Outbreaks of influenza occur almost yearly. Major disturbances tend to recur in cycles every few years. Because the severity and extent of an epidemic cannot be accurately predicted, annual vaccination is recommended. Certain categories of persons have a special need for protection. Characteristically, mortality from influenza and pneumonia is high in infants of less than one year of age, declines at later years of childhood, but after age twenty shows a progressive increase. After about sixty years of age, mortality exceeds that of infancy. At the extremes of life, then, influenza exacts a heavy toll. Furthermore, it has been repeatedly shown that during influenza outbreaks, mortality from chronic debilitating disease at all ages, i.e., chronic cardiovascular disease, chronic renal disease, and chronic pulmonary disease, is increased sharply above the usual levels. Clearly, influenza can tip the balance between life and death in persons whose continued existence is jeopardized by a serious chronic illness. The current experience with Asian influenza has emphasized again the fact that pregnant women are at increased risk of death from influenza, especially in the last trimester of pregnancy, and they, therefore, should be vaccinated promptly. Mortality, however, is not the sole standard by which the need for protection is judged. Because a high rate of illness might embarrass or prevent fulfillment of their mission, annual vaccination against influenza has been practiced by the Armed Forces for the past five years. In civilian life an incidence of 20 per cent or more in a community can seriously cripple its function and create a state of emergency. With this possibility in view, in 1957 the policy was formulated to urge vaccination of

civilians concerned with services essential to the normal maintenance of community activities; those concerned with health, public safety, public utilities and transportation.[3] To prevent overloading of facilities for medical care, vaccination has long been offered annually to students at certain colleges or at other institutions where people live together away from their homes. Finally, because a bout of influenza is an uncomfortable and inconvenient experience, there has been a growing use of influenza virus vaccine for protection of individuals regardless of their current state of health. Recently, the practice of vaccinating children has increased because of growing appreciation that the attack rate is at all times highest in childhood and that the child of school age frequently introduces infection into the home. Moreover, repeated infections of childhood probably exact their toll in the difficulties of later life.

Dose, Schedule and Route of Vaccination

These factors are varied by age because the practical and immunologic problems to be solved are not uniform at all ages. Vaccination of infants less than three months old is not recommended since in general they possess antibodies transferred transplacentally and ordinarily this antibody should afford adequate protection. After three months of age the maternally transferred antibody is lost, the infant's capacity to manufacture antibody upon primary stimulation remains poor, and, concomitantly, infants and young children are peculiarly sensitive to the toxic effects of influenza viruses. To minimize systemic reactions to vaccination and to take advantage of increased antibody response after larger amounts of virus are given in the initial course, the following plan of vaccination is recommended. From three months to school age, a dose of 20 to 40 CCA units of virus is given in 0.1 ml volume intracutaneously twice at one or two week intervals. At five to twelve years of age the child has usually had at least one previous infection with influenza A or B viruses and partial advantage can therefore be taken of the "booster phenomenon." At this age the child will also tolerate larger doses of influenza viruses. Hence, in this age group, adequate levels of antibody can generally be attained by giving 100 to 200 CCA units of virus subcutaneously, repeating the dose after an interval of one to two weeks. From thirteen years of age onwards, an adult dose of 400 to 500 CCA units given once subcutaneously is ordinarily prescribed. A range of dosage is given for each age group because the composition of influenza virus vaccines is varied from time to time according to current estimates of requirements for protection and availability of stocks of virus. It seems likely that the amounts of virus recommended for each age group will be revised upwards as experience accumulates because limited experience indicates that children can tolerate much larger doses than those described. Intracutaneous vaccination is not recommended for persons six years of age or older, because the smaller dose of vaccine that can be given intracutaneously results in a lower yield of antibody. Nor has there yet been a good field demonstration of the effectiveness of intracutaneous in comparison with subcutaneous vaccination. At present careful attention is being given to the usefulness of two doses of vaccine at intervals of six to eight weeks or longer even in adults, for the indications are that a broader and more durable resistance is developed. This subject is reviewed elsewhere.[4]

According to current information, the schedule of vaccination recommended for children three months to five years of age is well tolerated. The higher dose recommended for children five to twelve years of age may at times elicit systemic reactions in 10 to 20 per cent of those vaccinated. Malaise, muscle aches, headache, and chilliness are common symptoms of reaction. Fever is less frequently encountered. Nausea and vomiting occur rarely. It has been our practice to give acetylsalicylic acid to children as a prophylactic during the first twenty-four hours after vaccination, using the usual dose—age relationship as a guide; i.e., one grain of aspirin per year of age four times a day. With this procedure, experimental studies have been carried out safely in childen aged six to ten using 1000 CCA units given once subcutaneously. It would seem that oft voiced fears of the hazards of vaccination against influenza in childhood are largely unjustified. Persons receiving the adult dose experience systemic reactions at a rate of about one per cent. Persons known to be allergic to eggs should not be vaccinated. When in doubt, skin testing can be resorted to, using 0.02 ml of a one to ten dilution of vaccine.[5] A positive reaction is a wheal appearing in twenty to thirty minutes.

Adenovirus Vaccines

Adenoviruses cause acute respiratory disease of recruits (ARD), pharyngoconjunctival fever, and non-bacterial pharyngitis. These syndromes can occur in epidemic proportions under conditions of exposure seldom encountered in the civilian practice of medicine. Jordan, Price, and Evans have independently shown that infection with adenoviruses causes only a small proportion of the respiratory illness that occurs in civilian populations; i.e., between two and four per cent.[6-8] Therefore, despite the fact that adenovirus vaccines have been shown to be highly effective in the prevention of epidemic ARD among military recruits,[9-11] their use in civilian practice is not recommended at present.

Vaccination Against Respiratory Diseases Caused by Other Viruses

Isolation of new viruses from patients with respiratory illness is being reported at an encouraging rate.[12-15] Nevertheless, until the frequency and the consequences of infection by these recently described agents is known, and until evidence from carefully controlled vaccine trials establishes the value of prevention by vaccination, a conservative attitude towards the use of new but untried respiratory virus vaccines seems warranted.

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The Use of Nisentil in General Practice

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IN general practice, the need for a short-acting, well tolerated analgesic arises almost every day. Not only is such an agent required to relieve pain, it is also of value to encourage relaxation and facilitate prompt and precise completion of the procedure in question.

In the search for the ideal analgesic for office procedures and obstetric use, many preparations have been introduced, and a number of these have been used successfully. However, each has had its drawbacks and, up to this time, there has not been available a versatile and short-acting analegsic the general practitioner could use conveniently and safely in his office and obstetric practice.

A suitable analgesic must, among other things, be able to relieve pain and allay apprehension without causing loss of consciousness, nausea and vomiting or prolonged amnesia. Particularly when pain is severe, a primary concern of the physician is the administration of an adequate dose; this dose, however, must not be so large as to produce significant respiratory depression or other undesirable side effects.

This report deals with the use of Nisentil® Hydrochloride (alpha-prodine hydrochloride) for analgesia of short duration in a variety of procedures. Nisentil is a relatively new synthetic narcotic which provides effective relief of pain and apprehension with a minimum of side effects.[1-4] The respiratory depression which may follow the use of any potent analgesic can be prevented or effectively overcome by the concomitant administration of a narcotic antagonist such as Lorfan® Tartrate (levallorphan tartrate). Nisentil is rapid-acting and has a short duration of effect, features which make it particularly well suited to office and obstetric use.

First described by Ziering and Lee[6] in 1947, and introduced for clinical trial in 1948, Nisentil was subsequently used successfully in many thousands of patients. Earlier reports dealt mainly with the obstetric use of the drug. LaForge[7] achieved excellent results with Nisentil in 1,000 obstetric patients, and Kane[8] reported similar findings in another 1,000 patients. A number of other authors described equally good results in smaller groups. Recently, reported indications for Nisentil have expanded to include urologic procedures,[4,9,10,11] bronchography,[12] preoperative and postoperative analgesia,[2,3] and other conditions where a rapid-acting analgesic of relatively brief duration was required.

Although the series of cases here reported is small, the distribution of procedures effected is fairly wide and believed worthy of consideration. Nisentil was employed in eighty patients—thirty-five obstetric, eight orthopedic, three dental, thirty-three surgical and one postoperative.

Obstetric Procedures

In obstetrics, Nisentil was employed mainly during the second stage of labor. Observations on the use of Nisentil in the obstetric patient have been widely reported in the literature and need not be repeated here.[8,9,13,14] However, two additional advantages of Nisentil observed in this series appear to be significant and worthy of mention.

First, it was noted that when Nisentil was used in the second stage of labor—and sometimes in the more distressing portion of the first stage—the course of labor was materially shortened. Presumably, this was because of the relaxed condition and unimpaired co-operation of the patient.

Secondly, it was found that, because the second stage of labor was easier and shorter, the patient approached delivery with considerably less discomfort and tension. For example, in several multiparous patients who had had less effective analgesics for previous deliveries, delivery was far easier on this occasion. When these patients were given a 60 mg dose of Nisentil within the one and one-half hours before delivery, or 30 mg intravenously immediately before delivery, no other analgesics or anesthetics were required for delivery. On one occasion, the use of low forceps was well tolerated with Nisentil alone.

Orthopedic Procedures

In eight patients with fractures or dislocations, Nisentil was successfully employed for analgesia during manipulations. In two instances, the patients were children, both four years old, both with fractures of the forearm. One was a Colles' type fracture of the distal head of the radius, and the other was a green-stick fracture of both radius and ulna at the junction of the distal and middle third of the forearm. Both patients were given 30 mg of Nisentil intramuscularly and both fractures were comfortably reduced. These patients became very drowsy, but could be easily aroused at any stage of the procedure and were fully conscious of their surroundings when awakened.

The third fracture treated involved the supracondylar area of the right femur of a man forty-two years old. This patient also had an ununited fracture of the upper third of this femur, sustained previously, and an arthrodesis of the knee. Nisentil was administered in a dose of 30 mg intravenously, and reduction and immobilization of the supracondylar fracture was carried out without discomfort.

The fourth fracture treated in this manner was also manipulated under the influence of 30 mg of Nisentil intravenously. In this instance, the patient was a woman seventy-two years old, who had severely comminuted the distal head of the radius. She also had a contusion laceration over an incomplete ulnar fracture. Manipulation was without discomfort, but satisfactory reduction could not be obtained because of the comminution of the fragments. This patient was referred to an orthopedic surgeon for care.

Four other orthopedic patients were treated; two were elderly persons with fractures of the femoral neck. In the latter instances, 30 mg of Nisentil was administered intravenously to facilitate moving of the patients to and from the stretcher and x-ray table, and in both cases, excellent co-operation and excellent analagesia were obtained. The surgical fixation of these fractures was subsequently carried out under the usual anesthetic techniques.

One patient with a dislocation of the shoulder was treated with 30 mg of Nisentil intravenously. Although this dose permitted manipulation without undue discomfort, 120 mg of thiopental sodium by the intravenous route had to be given subsequently to secure adequate relaxation for reduction of the dislocation.

Reduction of a dislocation of the interphalangeal joint of the left thumb was accomplished under analgesia induced by 30 mg of Nisentil intravenously, and a laceration of the palmar surface of the thumb was sutured without further medication.

Dental Procedures

In three patients undergoing dental procedures, Nisentil was used in a dosage of 30 mg intravenously. One patient obtained excellent relief of pain during the filling of several cavities, but experienced nausea and vomiting. This reaction was attributed in part to the fact that she was in the second trimester of pregnancy. Two other patients underwent multiple extractions, but relief of pain and apprehension with Nisentil was only fair. These two patients were extremely apprehensive, and premedication with a mild barbiturate-atropine combination was not successful in allaying this apprehension.

Surgical Procedures

In twenty-two surgical procedures, Nisentil, in a usual dosage of 30 mg intravenously, was the only analgesic employed. When so used, ideally 100 to 200 mg of secobarbital or pentobarbital were given by mouth one hour before operation, together with 1 mg of atropine methylnitrate and 15 mg of phenobarbital to offset possible nausea. The procedures in which Nisentil was used alone for analgesia included a nasal polypectomy; evacuation of thrombosed external hemorrhoids; incision and drainage of a pilonidal abscess and other abscesses; the passage of urethral sounds; excision of hemorrhoidal tags; cystoscopy; debriding and dressing of burns; separation of a graft pedicle; direct laryngoscopy. In one four-month-old infant, a hemangioma was removed from the flank, after 20 mg of Nisentil I. M., without premedication.

Of particular interest as a demonstration of the efficacy of Nisentil was the performance of a dilatation and curettage for hemorrhage eleven days postpartum; this patient was given 30 mg of Nisentil intravenously and 4.5 grains of secobarbital intravenously, and received no other analgesic medication. She remained awake during the procedure and experienced no pain.

In the remaining eleven patients, Nisentil

was used in conjunction with other agents. Of six patients who had local anesthesia concomitantly with Nisentil, two underwent tonsillectomies for which the usual infiltration with 1 per cent procaine was carried out. It was found that the use of Nisentil with a local anesthetic resulted in a much less trying ordeal for the patient and an operation of shorter duration. The operations for which this combined analgesic medication was employed also included excision of a disfiguring scar; excision of a lipoma from the neck; and a sternal puncture for bone marrow studies. In each of these instances, 2 per cent procaine was used only in the skin, and dissection of subcutaneous tissue, where required, was performed with only the analgesia afforded by Nisentil. In every case, the patients were perfectly comfortable and did not complain of any pain.

Nisentil was also employed in conjunction with atropine (60 mg of Nisentil and 0.6 mg of atropine intramuscularly) as premedication for five patients about to receive general anesthetics, and as postoperative medication in one patient. The latter was a man, eighty-four years old, who had responded with profound respiratory depression to other analgesics.

Side Effects

In this series of eighty patients, there were only three instances of untoward side effects. In one woman, sixty-seven years old, who received 60 mg of Nisentil intramuscularly as preoperative medication, a mild degree of respiratory depression was noted during the administation of thiopental sodium. The four-month-old infant who had received an intramuscular dose of 20 mg of Nisentil developed a profound cyanosis, which was promptly terminated by the administration of 0.5 mg of Nalline (nalorphine hydrochloride) intravenously. One other case of cyanosis occurred in a newborn infant following the administration of a 60 mg dose of Nisentil to the mother about 20 minutes prior to delivery. This infant was promptly "pinked up" by the administration of 0.5 mg of Lorfan Tartrate (levallorphan tartrate) I.V.

In order to avoid the possibility of respiratory depression, which appears to be more prominent in the aged and the infant, it has become my policy to employ Lorfan Tartrate as a narcotic antagonist in such patients. Lorfan Tartrate has the ability to reverse the narcotic-induced respiratory depression without abolishing pain relief. It is mixed with Nisentil in a ratio of 1 mg of Lorfan to 60 mg of Nisentil. This ratio appears to afford the same protection as does the manufacturer's recommended 1:50 ratio, and has the advantage of permitting nurse or physician to use one ampul of each preparation, thereby avoiding errors in mixing. For obstetric use, the premixed solution is administered to the parturient woman.

Summary and Conclusions

Nisentil was employed as an analgesic in eighty patients in whom other analgesic agents had been demonstrated to be unsuitable, or in instances where lack of suitability was anticipated.

The analgesia produced by Nisentil was found to be adequate for a wide variety of surgical procedures, many of which would otherwise have required the administration of a general anesthetic.

The use of Nisentil was mainly free from undesirable side effects, with the exception of three cases of respiratory depression—two infants and one in an elderly patient.

This respiratory depression was promptly overcome with the use of a narcotic antagonist.

A method for the prevention of narcotic-induced respiratory depression by the combined administration of Nisentil and the narcotic antagonist Lorfan Tartrate is described.

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Granulocytopenia Associated with Chlorpromazine Therapy

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CHLORPROMAZINE APPEARS to be now established as a valuable pharmacological agent in the treatment of many medical conditions. Its use is widespread in hospitalized bed patients, as well as ambulatory patients. The drug has several side effects, the most serious of which is bone marrow depression with granulocytopenia. leukopenia developed in a number of patients but all of these recovered rapidly when chlorpromazine was discontinued. This particular group of borderline leukopenias is not included in this report. We concern ourselves here only with the six patients who developed severe granulocytopenia following the administration of chlor-

TABLE I. DURATION OF CHLORPROMAZINE MEDICATION BEFORE SYMPTOMS OF BONE MARROW DEPRESSION WERE DISCOVERED.
Data on six patients who developed granulocytopenia during Chlorpromazine medication.

Case	Age	Date Drug Started	Date Toxicity Discovered	Date	WBC	Granulocytes Per 100 Cells	Outcome	Date
1 V.W.	62	10-13	12-6	11-16	8050	(normal diff.)	Died	12-7
				12-6	1500	0		
2 G.B.	52	8-10	9-22	8-17	4850	48	Died	9-24
				9-22	100	2		
3 J.W.	68	3-28	5-1	5-1	250	0	Died	5-11
4 S.P.	35	5-29	6-18	6-4	5300	(normal diff.)	Recovered	
				6-18	3550	58		
				6-27	2800	12		
				6-29	2000	31		
				7-2	2900	29		
				7-12	7700	77		
5 F.M.	88	7-18	8-28	7-3	6000	(normal diff.)	Died	8-30
				8-21	4050	79		
				8-28	400	1		
6 M.C.	45	9-7	10-2	9-10	8200	(normal diff.)	Recovered	
				10-2	1300	44		
				10-3	1550	3		
				10-5	1750	2		
				10-9	2500	14		
				10-10	5300	19		
				10-11	9100	32		
				10-15	17900	70		
				10-17	13750	(normal diff.)		

The number of reports, reaching the literature, of granulocytopenia due to chlorpromazine is growing rapidly; suggesting that greater caution than hithertofore exercised, in its administration, is desirable and necessary.

Chlorpromazine has been used in this hospital (Northville State Hospital) on a mass basis, since October, 1954. Approximately 1,700 patients have received chlorpromazine, in varying dosages for varying periods of time, up to the present. Of these approximately 1,700 patients, six have developed severe granulocytopenia; four of these six having a fatal outcome. Mild, or questionable, promazine. They received from 50 to 100 mgm. of chlorpromazine three to four times daily.

Table I presents the pertinent data on these six patients. The four patients who died ranged in age from fifty-two to eighty-eight years. The two patients who recovered were below the age of fifty.

When the second fatality occurred, in September, 1955, the procedure of following up, hematologically, patients receiving chlorpromazine was reviewed and, at that time, the following policy was established: Complete white counts and differentials were obtained at the beginning of chlorpromazine medication and at periods of three, four, five, and six weeks after initiation of

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the medication. Thereafter, no white counts were taken unless the patient developed symptoms such as fever, sore throat, etc. Only the limited laboratory facilities of the hospital prevented us from seeking white counts at more frequent intervals. The particular time intervals between differential counts were established after screening the literature on chlorpromazine toxicity. Few reports had been made of the occurrence of granulocytopenia earlier than three weeks or later than seven weeks after the drug had been started.[1] Our experience has confirmed this observation. Leukopenia was discovered between twenty-five and fifty-three days after chloropromazine was started. The very first case of granulocytopenia, due to chlorpromazine, was discovered fifty-three days after the drug was started. Since the above policy had not been established at that time, there had been no white count for the three weeks preceding the discovery of leukopenia.

In Case 6, the patient had a normal white count three days after chlorpromazine medication was started. The second count was taken twenty-two days later and was 1,300 per cubic mm., with 39 per cent neutrophils. The following day, the neutrophil count had dropped to one and the second day had dropped to zero. It was evident that the leukopenia had developed suddenly and progressed rapidly. It was apparent that the leukopenic reaction began less than three weeks after chlorpromazine medication had been initiated.

Bone marrow studies were carried out in Cases 2, 3, and 5. They all demonstrated depression of the granulocytes and granulocytic precursors. In the four cases with fatalities, ACTH and cortisone were administered only a few days prior to death. In the two surviving patients, the white blood count started to improve two days and five days, respectively, after treatment with ACTH and corticoids was instituted. It is impossible to ascertain whether this improvement in the white count was a direct result of these drugs or due, primarily, to the discontinuation of chlorpromazine.

In a report to the A.M.A. Council on Pharmacy and Chemistry in January, 1956,[2] it is estimated that the rate of incidence of blood dyscrasia is very low in patients given chlorpromazine medication; possibly one in 50,000 to 100,000 patients receiving the drug. Our observations of six cases of bone marrow depression in a total of approximately 1,700 patients, suggests that the incidence of granulocytopenia, due to chlorpromazine administration, is considerably higher than this estimate. It would appear that this toxic reaction occurs much more frequently in patients over the age of sixty. Less than 10 per cent of the thorazine treated patients, in this hospital, have been above the age of sixty, yet half of the agranulocytic responses came from this age group. As noted previously, all patients in this older age group died. Bone marrow depression due to chlorpromazine appears to be much more serious in the older age group than in younger patients. We therefore feel that chlorpromazine and related compounds should be used with great caution in older patients. It has been our experience that granulocytopenia, if it develops, will occur between three and one-half and seven and one-half weeks after the initiation of medication. The rapidity with which granulocytopenia occurs is very alarming. Case 5 had a low normal white count of 4050 with a normal differential. Seven days later, this patient's total count was 400 per cmm., with a differential count of 1 segmented neutrophil, 88 lymphocytes, and 11 monocytes. This case demonstrates that weekly white blood count does not suffice as an accurate measure of beginning granulocytopenia. Ideally, counts should be done daily or at least every other day. They should be continued for at least two months after the initiation of chlorpromazine therapy. If a patient tolerates chlorpromazine without developing granulocytopenia for a period of at least two months, it appears probable that he will not develop bone marrow depression despite the continuation of the medication.

Case 4 was an epileptic and had been maintained on dilantin, 100 mgm., tid., at the time the neutropenia was discovered. The dilantin was not discontinued, and it is quite unlikely that this latter drug was responsible for the bone marrow depression, since the patient made a rapid recovery after chlorpromazine was discontinued. None of the other patients included in this report were receiving any drugs, other than chlorpomazine, which could be suspected as agents in bone marrow depression. None of these six cases of granulocytopenia developed jaundice. The concomitant occurrence of jaundice and granulocytopenia has been reported to be highly fatal.[3]

Summary

Six cases of granulocytopenia due to chlorpromazine are presented. Four patients above the

(Continued on Page 714)

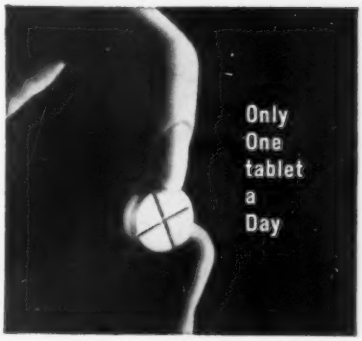
Low Dosage KYNEX for G.U. Infections

Unusual Antibacterial and Anti-infective Properties. More rapid absorption . . . higher and better sustained plasma concentrations . . . more soluble in acid urine than other sulfonamides . . . freedom from crystalluria and absence of significant accumulation of drug, even in patients with azotemia. [1]

Unprecedented Low Dosage. Less sulfa for the kidney to cope with . . . yet fully effective. A single daily dose of 0.5 to 1.0 Gm. (1 to 2 tablets) maintains higher plasma levels than 4 to 6 Gm. daily of other sulfonamides —a notable asset in prolonged therapy. [2]

New Control Over Sulfonamide-sensitive Organisms. KYNEX maintains the prolonged, high tissue concentrations of primary importance in treatment of urinary infections . . . a therapeutic asset toward preventing manifest pyelonephritis as a complication of persistent bacteriuria during pregnancy and puerperium. Maintenance of sterile urine in such patients was accomplished with 1 tablet of KYNEX daily. [3]

KYNEX*



Sulfamethoxypyridazine Lederle

Dosage: The recommended adult dose is 1 Gm. (2 tablets) the first day, followed by 0.5 Gm. (1 tablet) every day thereafter, or 1 Gm. every other day for mild to moderate infections. In severe infections where prompt, high blood levels are indicated, the initial dose should be 2 Gm. followed by 0.5 Gm. every 24 hours. Dosage in children, according to weight; i.e., a 40 lb. child should receive ¼ of the adult dosage. It is recommended that these dosages not be exceeded.

KYNEX—WHEREVER SULFA THERAPY IS INDICATED

Tablets: Each tablet contains 0.5 Gm. (7½ grains) of sulfamethoxypyridazine. Bottles of 24 and 100 tablets.

Syrup: Each teaspoonful (5 cc.) of caramel-flavored syrup contains 250 mg. of sulfamethoxypyridazine. Bottle of 4 fl. oz.

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*Reg. U. S. Pat. Off.

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Congenital Inadequacy of the Cervix as a Cause of Infertility

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FACTORS responsible for successful termination of sterility cases studied in our office proved that patients falling in the relative infertility group had opened a channel of investigation leading to one of the specific causes of premature delivery in the nullipara. This is the problem presented by the pathological lower uterine segment which we* feel is of congenital origin.

From this review, the women in the above categories revealed pathology amenable to corrective treatment as follows:

First, by preventive therapy in thirteen prima gravidas with congenital inadequacy of the cervix. Early recognition made it possible to deliver 11 viable babies, thus avoiding neonatal death and a subsequent relative infertility.

Second, by preventive therapy in ten of the nineteen multigravidas who by history have congenital inadequacy. In these women investigation revealed that *of* their multiple early deliveries, the first one terminated prematurely without traumatic incidence to the cervix.

Third, by the use of the Lash technique or its modification in the tracheoplasty operation in fifteen of the above women.

The author encountered his first problem of the inadequate cervix twenty-two years ago and subsequently has had moderate success by conization of the internal os as Steinberg[16] reported at the International Fertility Association meetings in Naples in 1956. This procedure has been replaced by a modification of the Lash tracheoplasty technique.

From a survey of the literature and discussion with fellow practitioners of the causes and treatment of premature delivery, one suspects a lack of understanding of cervical inadequacy as one of the multiple and complex causes of early termination of pregnancy.

In a study of the modern textbooks, it was noted that Greenhill,[6] Eastman,[3] and Titus[18] were the only authors writing in detail of this important facet of the problem of premature labor.

Therefore, those of us working in obstetrics and infertility should be grateful to Dr. Abraham Lash for bringing into focus the problems of a group of relatively infertile women in whom no endocrine or wheat-germ routine would prevent an early delivery.

The definitive diagnosis and surgical correction of the incompetent cervical os was first correlated by him from the world literature which included the investigations of J. J. Fisher,[5] personal communications with N. Sproat Heaney as quoted by Dr. Lash,[7] and the studies of Palmer[11,12] and Lacomme.[11] Lash was distressed by the paucity of literature available during the past twenty-five years on this subject of second trimester abortion due to the incompent cervix. The material was summarized in his two important papers, i.e., Lash and Lash, 1950,[7] and Rubovits, Cooperman, and Lash, 1953.[15]

The senior Dr. Lash, reporting to the International Infertility Association in Naples in May, 1956,[6] discussed the results of 44 tracheoplastics for this type of habitual abortion. He was able to follow thirty-four of these patients, showing viable pregnancies after surgery in twenty-nine (85 per cent).

However, in the original work of Lash and that of the few other men who report this problem, the traumatic factors of previous pregnancy, abortion, and cervical trauma were given as the predominant causes. A characteristic statement was, "In virtually all of our cases there was an antecedent history of trauma to the cervix.[15]"

In our study of patients with inadequate cervices, it was found that 32 per cent had had no previous pregnancy, abortion, or curettage. These cases without forewarning had lower uterine segments which became completely effaced and dilated early in the second trimester. We believe these are the women who have a congenital inadequacy of the cervix. When not detected, they

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will continue to contribute to the high premature death rate because of repeated early termination of pregnancies resulting in relatively infertile marriages. In our work we became aware that by frequent vaginal examinations we were able to detect the early effacement of the cervix. This occurs over an extended period of time in preparation of the uterus for premature delivery. This is in agreement with the recent publication of work done on the "Prevention of Premature Delivery" as reported by Dr. L. J. Stephens.[17] The definitive diagnosis must be made early and the proper treatment instituted if the pregnancy is to be carried at least to viability.

The importance of this problem of premature delivery in our state is emphasized by the following facts as reported by Dr. G. Corneliuson of the Michigan Department of Health: "(a) Prematurity is still the greatest cause of death in children; and (b) Prematurity ranks 7th as a cause of all deaths."[2]

Majewski and Jennings bring us abreast of the times in stating that between 6 and 7 per cent of the total United States births have been consistently premature.[9]

Great strides have been made in the past ten years in the reduction of neonatal death rates by the improved obstetrical care of the newborn. This has been accomplished largely by the work of Beck[1] and Potter[13,14] in emphasizing the responsibility of the obstetrician for the first twenty-four hours of the infant's life.

By 1950, the year that terminated my ten-year study of peri-natal morbidity and mortality at Crittenton General Hospital in Detroit,[19] it was possible to cut our rate by almost 50 per cent because of improved antenatal, intrapartum and postpartum care. At that time my attention was focused upon a discouragingly large group of the second trimester deaths of no known cause except prematurity.

Since then, the percentages in Michigan have remained almost static. In 1950, the neonatal death rate was 6.6 per 1,000. In 1955 it was 6.4. In 1955 there were 14,000 premature births or 7.3 per cent. This group accounted for 49 per cent of the fetal deaths.[2]

The author believes that early diagnosis of the inadequate lower uterine segment by all men practicing obstetrics would start a new trend which could change this figure to one which will begin to approach the irreducible minimum, as we are now experiencing in maternal mortality statistics.

The ideal method for the further reduction of the above figures as discussed by Potter[13] is a prophylaxis against the early delivery, thus circumventing the difficult task of caring for the immature infant.

In our office, one method used for preventing the premature delivery is the early diagnosis of the congenital inadequacy of the cervix. This has been facilitated by the fact that these women are infertility case studies and a complete investigation offered clues that they should be followed more closely than the routine pregnancies.

In the prima gravida group, it was noted that only one out of thirteen demonstrated abnormal hormone assays.

In the multigravida group, there were nineteen with relative infertility because of repeated premature terminations of pregnancy. Careful analysis of their histories including hospital records revealed no trauma to the lower uterine segments. When beginning treatment at our office, these women had a total of forty-seven conceptions with only a 20 per cent fetal salvage because of an apparent inadequate lower uterine segment. We, therefore, consider them to be a badly neglected congenital type.

The following signs and symptoms were found in the majority of all cases:

1. The examination revealed a 5/6 to 1/6 corpus to cervical ratio or a combination of hypogenital characteristics.

2. Ethiodal studies revealed that in a majority of the patients there is an abnormal uterine contour. The predominate variation presented is an arcuate type with a tendency to the bicornuate pattern. There is a subsequent loss of the normal cervicocorpus angle which gives the cavity a truncated appearance.

Dr. Frederick Falls in a recent discussion of a paper on the cause of premature delivery stated that following a good many years of study of the configuration of the uterus he finds a rather large percentage of abnormalities in habitual abortion problems.[4]

3. The Basal Body Temperature variations were minimal and nonconstant in the majority of these cases, offering a clue to an approaching problem. No amount of hormones changed the temperature patterns. One patient took 450 milligrams of oral progesterone per day for 26 weeks.

4. Lower abdominal pressure, excessive painless uterine contractions, persistent dysuria, and rectal irritability were premonitory findings which could not be ignored if the diagnosis were to be made early.

5. Fetal movement becomes quiet from increased intra-uterine tension once effacement and dilatation occur.

Suspected patients are carefully instructed and asked to advise us when any one of the preceding conditions occurs. Speculum and vaginal examinations are mandatory in these women every five to seven days beginning in the second trimester. The definitive diagnosis is made on feeling and seeing complete effacement and at least 2 or 3 centimeters of cervical dilatation with the membrane presenting.

The inadequate cervix should be detected before the membrane is extruded through the os into a sphere because when this does occur, the total intra-uterine volume is diminished, the cervix contracts, and shearing of the placental bed may result in uterine bleeding before the rupture of the membranes. This leads to a confusion in diagnosis of the true etiology causing the termination of pregnancy.

The membrane may present as a hemisphere as visualized in twenty of our cases of the inadequate cervix. With treatment relieving the hydrostatic pressure on the segment, the secundines will retract and the cervix close. Our experience has proved that this is a type of threatened abortion for which bed rest is one of the remedies.

Our first method of treatment then is that of preventive therapy in order to circumvent the early delivery:

1. Bed rest, high Trendelenburg, until the cervix closes
2. Bathroom and laxative privileges
3. Prophylaxis against intra-abdominal pressure
4. Carefully adjusted maternity corset
5. Lutrexin tablets, 4 STAT—three, two, one each hour until the contractions and uterine tension decrease in those patients with uterine irritability.
6. House calls
7. Termination of pregnancy by appointment to avoid a precipitous home delivery.

We have used Lutrexin since its introduction to the market.* Patients have been instructed when and how to use this medication and to tabulate its effectiveness. Of the women given this preparation, 55 per cent report their ability to control the uterine contractions and symptoms with this drug.

After the cervix has closed, the membrane retracted, and the patient has a viable baby, she is given liberty commensurate with the adequacy of the cervix.

Following the above routine in the thirteen nulliparous women who had eighteen pregnancies with congenital inadequacy of the lower uterine segments, eleven infants (60 per cent) were carried to viability and survived. In seven patients the membranes ruptured before the twenty-sixth week resulting in fetal deaths.

In the multigravida group who had had a previous fetal salvage of 20 per cent, early visual diagnosis was made in ten cases. Of these babies, 80 per cent survived on the above conservative treatment.

We realize that when bed rest might be necessary for as long as six months it may be extremely difficult for our patients. Therefore, we recommend tracheoplasty following delivery in all who have had a positive diagnosis by visual and digital examination of cervical inadequacy during pregnancy and confirmed by ethiodol studies.

We also recommend surgery for the women in whom the abnormality exists, proven by history and the Lash x-ray technique.

During the weeks that this paper was being completed, a woman in the above group who had successfully carried her last of five pregnancies to viability on conservative therapy, presented us with a second effacing dilating cervix at twenty-two weeks. Bed rest was impossible and, following a discussion with Dr. W. J. Mulligan,[10] it was decided to take a more positive approach to prevent the premature rupture of the membrane. Following his technique, a polyethylene (animal tested) 1/16 inch tubing was used as a purse string suture to close the cervix.

The writer believes that this definitive approach used in the early months of gestation in the women who have bad histories of habitual abortion of this type would result in greater fetal salvage.

When indication for operation is not well defined, we prefer to observe the patient through a pregnancy before surgery.

We have used tracheoplasty in fifteen women. Six of these have not attempted to conceive. Seven have become pregnant and all have carried to term except one. This patient had a poor result from surgery and delivered a 3½ pound premature viable baby. Two who have conceived are in the third trimester with no forseeable difficulty.

*Hynson, Westcott & Dunning, Inc., Baltimore, Maryland. Patients using Lutrexin were on individual prescription basis.

The purpose of this paper is to emphasize three important factors:

1. The possible fetal salvage by the early recognition of the congenital inadequate lower uterine segment as a definite entity causing prematurity and relative infertility.

2. To further stimulate all doctors practicing obstetrics to use the simple inexpensive diagnostic device of more vaginal examinations in the second trimester.

3. To prove there is a positive approach to avoiding infertility and fetal wastage by a direct attack upon the consistent 7 per cent premature birth rate which resulted in 1200 neonatal deaths in Michigan in 1955.[2]

Acknowledgment

Gratitude is expressed to Drs. R. C. Jeremias and J. L. Gillard, my partners, who have spent many hours examining the patients cited in order to establish that congenital inadequacy of the cervix is a definite clinical entity as a cause of prematurity and relative infertility.

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GRANULOCYTOPENIA WITH CHLORPROMAZINE

(Continued from Page 710)

age of fifty died, while two younger patients recovered. The much higher incidence of this complication in the older age group, together with the fatal outcome in these patients, indicates caution in the use of chlorpromazine in this age group. In each instance, the granulocytopenia was discovered twenty-five to fifty-three days after chlorpromazine therapy was initiated. In one case, blood changes developed very rapidly with a white count of only 400 with one granulocyte within a week after a preceding normal count had been obtained. The incidence of six cases of thorazine granulocytopenia, in a total of approximately 1,700 patients receiving the medication, indicates a much higher frequency of this complication than has generally been recognized. It is recommended that for the first eight weeks white blood counts be done daily or at least every other day.

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Musculoskeletal Manifestations of Systemic Lupus Erythematosus, Polyarteritis Nodosa, Dermatomyositis and Diffuse Scleroderma

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IN A RECENT symposium, Robb-Smith reviewed the historical evolution of the concept of connective tissue as a functioning unit subject to specific diseases. This concept was first introduced by Klinge in connection with rheumatic fever and rheumatoid arthritis and became widely known when Klemperer, Pollack and Baehr described disseminated lupus erythematosus and diffuse scleroderma as diffuse collagen diseases. Polyarteritis nodosa and dermatomyositis have subsequently been added to the list of connective tissue diseases. Although the term collagen (or connective tissue) disease has no diagnostic significance, its introduction has served to stimulate investigation of these disorders and of connective tissue.

Klinge and Vaubel pointed out the similarity between some of the lesions of rheumatic fever and polyarteritis nodosa and those which could be induced in experimental animals by the injection of foreign protein. Others have suggested, on the basis of certain common histologic features, including fibrinoid necrosis, that all of the diseases of this group may have an allergic or hypersensitive origin. However, the nonspecific nature of fibrinoid necrosis has been emphasized repeatedly. Further, it has been recognized that connective tissue can respond to injury only in a limited number of ways. Duff has described these as formation of excessive and possibly abnormal matrix within which fibrinoid necrosis may occur, proliferative activity of fibroblasts with production of new collagenous connective tissue, and granulomatous inflammatory reaction. Variations in the degree of participation of these components and differences in anatomic distribution enable the pathologist to distinguish the various disease entities in most cases. At present an allergic mechanism appears probable in serum sickness, rheumatic fever, and at least some cases of polyarteritis nodosa. One must conclude, however, that although similar morphologic features are perhaps suggestive of a similar pathogenesis, they are by no means conclusive proof.

Since connective tissue is a constituent of every body tissue and organ, it is not surprising that these diseases exhibit a wide variety of signs and symptoms and in many cases present overlapping or shifting clinical pictures. Musculoskeletal manifestations are prominent among the features which these disorders may share. Indeed, such manifestations occur almost without exception in rheumatoid arthritis and are present in a majority of cases of rheumatic fever. The recent report of Friedman, Schwartz, Trubek, and Steinbrocker served to re-emphasize the arthropathies associated with the other ("pararheumatic") connective tissue diseases.

The study was undertaken to review the experience at the University of Michigan Hospital with systemic lupus erythematosus, polyarteritis nodosa, dermatomyositis and diffuse scleroderma. It was restricted to necropsy cases, in order to avoid uncertainty regarding the clinical diagnosis and with the expectation of obtaining material from the articulations. Unfortunately, insufficient material was available to permit any comment regarding the histopathologic changes in the synovial tissues. Particular attention was directed to the

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frequency and type of musculoskeletal manifestations and to points of possible value in the differential diagnosis of these disorders.

Systemic Lupus Erythematosus

Musculoskeletal manifestations have been amply recognized as one of the most frequent manifestations of systemic lupus erythematosus. In report of 154 cases seen at the Mayo Clinic prior to 1938, Montgomery described "arthralgia or arthritis" in 63 per cent of the acute cases, 57 per cent of the subacute, and 20 per cent of the chronic cases. In a review of 132 cases seen at the same institution from 1939 through 1947, Montgomery and McCreight noted "arthralgia or arthritis" in 91 per cent of acute, 71 per cent of subacute, and 43 per cent of chronic cases. This apparent increase in incidence was attributed to an increased awareness of articular symptoms as an early manifestation of the disease. Harvey, Shulman, Tumulty, Conley and Schoenrich reported "arthritis or arthralgia" in 90 per cent of 105 patients seen at Johns Hopkins Hospital; in 32 per cent an "acute migratory polyarthritis" was the initial manifestation of illness. These authors comment that striking objective joint changes are less common than the complaint of arthralgia with mild soft tissue swelling but without redness or much local tenderness. Soffer, Elster and Hammerman reported similar findings in a review of thirty-two patients; symptoms of "arthralgia" occurred in 94 per cent of the cases and "arthritis" in 59 per cent; in 44 per cent actual joint abnormalities were demonstrated on physical and roentgenologic examination.

Most authors have recognized that, although subjective musculoskeletal complaints are perhaps most frequent, a considerable proportion of cases will have objective joint findings. In some there may be migratory involvement of the large or small joints closely simulating rheumatic fever. In a smaller group of cases there occur deformities, contractures, ankyloses, and x-ray changes compatible with rheumatoid arthritis. Harvey and associates "observed that skeletal deformities were frequently associated with chronic arthritic involvement." These were described as "typical of rheumatoid arthritis" in 28 of 95 patients with joint involvement. Contractures, muscle atrophy and joint deformity were occasionally marked and at times disabling. Shearn and Pirofsky found deformities "similar to the changes observed in rheumatoid arthritis" in 12 per cent of 34 cases. Dubois stated that "arthritis is the most common presenting symptom" and "is usually typical of early rheumatoid involvement." A "persistent rheumatoid deformity" occurred in 30.6 per cent of his 62 cases. Dubois concluded, "as far as one can tell, both clinically and pathologically the arthritis is indistinguishable from the idiopathic type of rheumatoid involvement." In our opinion, it is difficult to judge whether such cases are examples of systemic lupus erythematosus alone or whether they represent the coexistence of this disease with rheumatoid arthritis.

Musculoskeletal symptoms represented the initial manifestation in eight (38 per cent) of the present group of twenty-one patients and occurred ultimately in eighteen (86 per cent). Arthralgia and/or myalgia was unaccompanied by objective joint findings in seven (33 per cent). Objective evidence of active synovitis was observed in eleven (52 per cent). Physical findings in regard to the joints were usually mild and transient, but in five cases were sufficently severe and persistent to suggest rheumatoid arthritis to experienced observers. Flexion contractures of moderate degree developed in three patients: these involved, respectively, the knees, elbows and fingers, and fingers alone. In four cases the migratory pattern of joint involvement was suggestive of rheumatic fever. These observations are summarized in Table I.

Polyarteritis Nodosa

Harris, Lynch and O'Hare reviewed 101 cases of polyarteritis nodosa and reported "arthritis" in 27 per cent; in many instances, undoubtedly, joint pain was the only manifestation of articular involvement. Logue and Mullins in a similar review of 177 reported cases, noted the occurrence of "arthritis" in 34 per cent. These authors stated that "muscle pain and soreness are common," that "joint symptoms are frequent and vary from arthralgia to acutely swollen joints," and that "migratory polyarthritis may occur." Boyd reported "joint involvement" to be the initial manifestation in fourteen of 100 cases and the second in eleven; the neuromuscular system was involved first in nineteen cases, second in eight, and third in four. This author commented on the tendency of articular and neuromuscular symptoms to appear early, but observed that the joint symptoms

tended to fade into the background as the disease progressed, and that late in the course inspection of the joints usually proved negative even though arthralgia persisted. Mowrey and Lundberg, sided leaving muscle atrophy, loss of joint motions and moderate flexion contractures which closely simulated rheumatoid arthritis. X-ray examination of the hands and wrists revealed only osteoporosis.

TABLE I. MUSCULOSKELETAL MANIFESTATIONS IN FIFTY CASES OF CONNECTIVE TISSUE DISEASE

	Systemic Lupus Erythematosus 21 cases	Polyarteritis Nodosa 18 cases	Dermatomyositis 5 cases	Diffuse Scleroderma 6 cases
Initial manifestations of disease	8 patients, 38%	4 patients, 22%	1 patient, 20%	5 patients, 83%
Arthralgia and/or myalgia, without objective findings	7 patients, 33%	10 patients, 55%	3 patients, 60%	6 patients, 100%
Polyarthritis	11 patients, 52%	4 patients, 22%	0 patients, 0%	0 patients, 0%
R.F.-like	6 patients, 29%	2 patients, 11%		
R.A.-like	5 patients, 24%	2 patients, 11%		
Flexion contractures	3 patients, 14%	2 patients, 11%	2 patients, 40%	6 patients, 100%
No musculoskeletal manifestations	3 patients, 14%	4 patients, 22%	2 patients, 40%	0 patients, 0%

in a recent review of 607 cases from the literature and at the Armed Forces Institute of Pathology, stated that "musculoskeletal manifestations" occurred in 50 per cent. Lowman found muscle and joint symptoms early in the course of thirty of forty-three cases; however, only four had objective evidence of synovial involvement. This author stated that the muscular symptoms were usually worse with activity and better with rest, in contrast to the symptoms of generalized fibrositis which are usually worse after rest and relieved by activity.

In eighteen patients in the present study,* musculokeletal symptoms were the initial complaint of four (22 per cent) and were present at some time in fourteen (78 per cent). Ten patients (55 per cent) had symptoms of stiffness, aches, or pains in joints and muscles without accompanying objective physical findings. Polyarthritis, with objective joint findings, occurred in four instances and was confused with symptoms of rheumatoid arthritis or rheumatic fever.

The first patient was a twenty-three-year-old woman whose illness began with an acute polyarthritis involving the knees, wrists, metacarpalphalangeal and proximal interphalangeal joints. After several months the process gradually subsided leaving muscle atrophy, loss of joint motions and moderate flexion contractures which closely simulated rheumatoid arthritis. X-ray examination of the hands and wrists revealed only osteoporosis.

The second patient was a thirty-nine-year-old man who developed mild swelling and tenderness and aching of the larger peripheral joints one year after the onset of his illness. A diagnosis of rheumatic fever was suggested by a physician, and large amounts of salicylates were administered with only moderate relief. Gradually, marked muscular atrophy and flexion contractures of the elbows, wrists and finger joints developed. The wrists became ankylosed.

The third patient was a fifty-year-old man whose illness began when he awoke one morning with swelling, redness and increased warmth and pain on motion in the proximal interphalangeal finger joints, wrists, elbows, shoulders, ankles, knees and hips. The patient's temperature varied from 99 to 100 degrees F. and a tentative diagnosis of rheumatic fever was made. All joint manifestations subsided during a three week period of bed rest.

The fourth patient was a forty-six-year-old man who developed swelling, erythema, and increased warmth of the left knee. There was marked subjective and objective improvement following a one month course of therapy with cortisone, 50 mg. daily.

Dermatomyositis

A review of the literature confirms the view that, although subjective musculoskeletal complaints are common, objective evidence of intra-articular disease is rarely found in association with

*Specifically excluded from the present study were four patients with well established rheumatoid arthritis who developed diffuse arteritis similar in many respects to polyarteritis nodosa. An additional four cases in which minimal localized arterial lesions were associated with hypertensive renal disease were also excluded.

dermatomyositis. O'Leary and Waisman found "arthritis" presumably with objective joint findings, in two of forty cases. Sheard reported joint stiffness and periarticular swelling in seven of twenty-five patients with dermatomyositis; the hands, elbows and knees were chiefly involved. In three of these patients, there were objective joint changes in the hands which were stated to be similar to those of rheumatoid arthritis. In a clinicopathologic conference, Lever discussed a case of proven dermatomyositis with x-ray evidence of joint damage which he attributed to coincident rheumatoid arthritis. In most reported cases muscular symptoms have been prominent; these include aching, stiffness, tenderness, cramps, weakness and atrophy. Involvement of the extrinsic ocular muscles, diaphragm and muscles of the larynx, pharynx and anal and vesical sphincters has been described. Flexion contracture and joint deformity may occur. Such changes have been attributed to involvement of muscle, tendinous insertions and periarticular supporting structures.

Muscular involvement dominated the clinical picture in the present group of five patients. Early symptoms included stiffness, tenderness and aching. As the disease progressed, atrophy and weakness became prominent. Arthralgia was present in three cases, although other evidence of inflammatory intra-articular disease was not observed. Persistent contractures of 30 to 70 degrees of elbows and knees developed in two patients.

Diffuse Scleroderma

The literature concerned with scleroderma contains scattered references to the occurrence of musculoskeletal manifestations. Osler in a detailed report of eight cases, described arthritic symptoms in five. O'Leary and Nomland reported mild to severe degrees of stiffness, aching, tenderness and occasional swelling in the joints of 58 per cent of forty-eight patients with generalized scleroderma. X-ray examination of the hands was made in sixteen of the twenty-eight cases with joint complaints and was normal in six; "periarticular arthritis" (presumably soft tissue swelling) was marked in four and slight in one case; destructive changes of the bones of the hands were present in two and loss of some or all of the distal phalanges in three. Gil reported eight cases of diffuse scleroderma, four of which "showed clinical manifestations of arthritis" which cleared after weeks or months leaving no residue; x-ray examination of these patients revealed no joint abnormality. It has been recognized, however, that persistent joint deformities may occur in scleroderma. Sellei, in his discussion of acrosclerosis, states that the hands tend to assume an "inwardly-bent position" due to flexion of the fingers and that in some cases "changes," which he does not describe, appear in the joints ("pseudoarthritis deformans"). Leinwand, Duryee and Richter, reporting 150 cases, stated that joint pain was almost always present and often preceded the skin changes, so that arthritis was not uncommonly an early diagnosis. Contracture deformities were also noted in their cases. Rodnan, Black, Bollet and Bunim have recently reported six patients with diffuse scleroderma, three of whom were stated to have "complaints of sore, swollen joints, with involvement of virtually all the peripheral articulations." They found evidence of an acute or chronic inflammation in the synovial tissue obtained by open biopsy of the suprapatellar bursae of these three patients. In addition, x-ray examination disclosed osteoporosis and narrowing of the joint spaces.

The initial complaint of five of the six patients with diffuse scleroderma in the present series was swelling, stiffness and pain in joints. Such symptoms often antedated definite skin changes and were confused with symptoms of early rheumatoid arthritis in four instances. Despite lack of evidence of intraarticular disease, loss of motion and mild flexion deformity developed in all cases.

Differential Diagnosis

Musculoskeletal involvement in these fifty patients frequently resulted in confusion with rheumatoid arthritis or rheumatic fever. Differential diagnosis was often difficult and at times impossible except with the passage of time and appearance of additional manifestations.

Rheumatoid Arthritis.—The clinical picture of rheumatoid arthritis is dominated by the joint manifestations; usually these overshadow the constitutional and extra-articular manifestations, although recent reports of "malignant rheumatoid arthritis" emphasize that this is not invariably so. Joint involvement is usually symmetrical, progressive and when well established readily recognizable. So-called "atypical" cases, however, are

common and may be readily confused with the other connective tissue diseases. The presence of subcutaneous nodules constitutes a most helpful diagnostic sign. These nodules, which may occur in 20 to 30 per cent of cases, are generally considered to be the most specific pathologic lesion of rheumatoid arthritis. Renal involvement, which is common in systemic lupus erythematosus and polyarteritis nodosa, is extremely rare in uncomplicated rheumatoid arthritis. Although ocular involvement may occur with any of the connective tissue diseases, Godtfredsen stated that uveitis and episcleritis are more characteristic of rheumatoid arthritis, while exudative or hemorrhagic retinopathy is more frequent in systemic lupus erythematosus and polyarteritis nodosa. Hypertension is uncommon in rheumatoid arthritis, unusual except as a late manifestation in systemic lupus erythematosus and relatively common in polyarteritis nodosa. Although hemagglutination tests are being perfected, there is at present no laboratory test that can be considered diagnostic of rheumatoid arthritis.

Rheumatic Fever.—Rheumatic fever occurs most commonly in children and young adults. Its pathogenesis is intimately linked with preceding hemolytic streptococcal infections. Antibodies against various streptococcal products can be demonstrated in higher than normal titer in the sera of patients with early rheumatic fever. A variety of nonspecific "acute phase reactions," such as the presence of C-reactive protein and elevation of the erythrocyte sedimentation rate, may also be present. The diagnosis is favored by the presence of two or more of the major Jones criteria as modified by a committee of the American Heart Association: carditis, typical polyarthritis, chorea, subcutaneous nodules, or erythema marginatum. Joint involvement is quite characteristic; one or several joints may be affected at a time, usually in a rapidly migratory fashion and with complete clearing without residual damage. Cardiac involvement is more frequent and more severe than in the other connective tissue diseases. Prolongation of the P-R interval in the electrocardiogram is a common finding in early acute rheumatic fever. The presence of chorea is of great diagnostic value, since it is almost exclusively a manifestation of rheumatic fever. Erythema marginatum, although it occurs in only about five per cent of cases, is likewise considered a relatively specific lesion. The subcutaneous nodules of rheumatic fever differ from those of rheumatoid arthritis in their small size, brief duration, and histologic appearance.

Rheumatic fever is most apt to be confused with rheumatoid arthritis and systemic lupus erythematosus. The features outlined above, however, suffice for differentiation in most cases. The absence of persistent or residual joint involvement is in sharp contrast to the usual findings in rheumatoid arthritis. Response to adequate doses of salicylates is as a rule more prompt and complete than in rheumatoid arthritis or the other disorders of this group.

Systemic Lupus Erythematosus.—In systemic lupus erythematosus the constitutional and extra-articular symptoms ofter overshadow the joint symptoms and not uncommonly may increase in severity at a time when joint manifestations are subsiding. In rheumatoid arthritis the articular and extra-articular manifestations usually proceed in a parallel fashion. Renal involvement, which is not encountered in uncomplicated rheumatoid arthritis, often occurs in systemic lupus erythematosus. Other findings expected in a sizable percentage of cases of systemic lupus erythematosus, but unusual in rheumatoid arthritis, include: erythematous eruptions of the face, involvement of the nonarticular serous membranes with effusion, central nervous system involvement as manifested by convulsions or toxic psychoses and clinical evidence of cardiac disease. Notable leukopenia is present in the majority of cases of systemic lupus erythematosus, where as it is relatively uncommon in rheumatoid arthritis and distinctly unusual in acute rheumatic fever or polyarteritis nodosa. Leukocytosis, common in the latter two diseases, is uncommon in systemic lupus erythematosus in the absence of intercurrent infection. False positive serologic tests for syphilis have been reported in up to one-third of cases of systemic lupus erythematosus but have not been described with increased frequency in the other diseases of this is generally regarded as specific, although there are group. The lupus erythematosus phenomenon is generally regarded as specific, although there are reports of occasional false positive tests in a variety of other conditions, including rheumatoid arthritis. Biopsy of characteristic skin lesions may be of diagnostic value and, in an occasional case,

microscopic examination of material obtained by punch biopsy of the kidney may provide the diagnosis.

Systemic lupus erythematosus may occasionally simulate dermatomyositis although muscular symptoms are invariably much milder and atrophy, when it occurs, usually involves the small muscles of the hand rather than the large proximal muscle masses. Systemic lupus erythematosus rarely involves the extrinsic ocular, laryngeal, pharyngeal or palatal muscles, or diaphragm, all of which may be involved in dermatomyositis. Periorbital edema frequently occurs early in the course of dermatomyositis, whereas in systemic lupus erythematosus it is usually a late manifestation associated with renal impairment.

Polyarteritis Nodosa.—Polyarteritis nodosa conforms to no distinctive clinical pattern. Its most characteristic feature is the serial involvement of multiple organs or systems, often producing a highly variable or bizarre clinical picture which cannot be conveniently fitted into conventional diagnostic categories. The diagnosis should be seriously considered in the following situations: (1) a patient with bronchial asthma who develops eosinophilia in excess of 25 per cent, (2) a patient with hypertensive renal disease who develops constitutional or other symptoms not readily explained by the original diagnosis, and (3) a patient with apparent rheumatoid arthritis who develops severe constitutional symptoms or extra-articular involvement and pursues an abrupt downhill course. The occurrence of any of the following signs or symptoms should suggest the diagnosis, especially if associated with one of the aforementioned clinical situations: peripheral neuritis, abdominal pain, peptic ulcer, unexplained gastrointestinal bleeding, hypertension, palpable nodular lesions along the course of superficial arteries, necrotizing skin lesions, abnormal urinary findings, intermittent testicular pain, Loeffler's syndrome, x-ray picture of "diffuse granular disease" of lung, persistent unexplained polymorphonuclear leukocytosis, or a recent history of serum sickness or reaction to sulfa drugs or penicillin. The ultimate diagnosis is based on histologic examination; muscle biopsy can be expected to yield a positive diagnosis in 30 per cent or more of cases. It must be emphasized, however, that a negative muscle biopsy is of no value in excluding the diagnosis. When a reasonable suspicion exists regarding the diagnosis, multiple muscle biopsies should be obtained.

Dermatomyositis.—The primary clinical manifestations of dermatomyositis are those in skin and muscle. The skin lesions may be indistinguishable from those of systemic lupus erythematosus. Often, however, early in the course of dermatomyositis there is facial or periorbital edema, which is usually a late finding related to renal impairment in systemic lupus erythematosus. There may be confusion with diffuse scleroderma since induration and atrophy of the skin may occur in dermatomyositis and impressive muscular involvement is occasionally present in scleroderma. Subcutaneous calcification is relatively common in both of these disorders, but rare in the other members of this group. In dermatomyositis the combination of muscle tenderness, aching, weakness and atrophy is more severe than in the other connective tissue diseases. Likewise, involvement of the extraocular muscles, diaphragm, or muscles of the larynx, pharynx or anal or vesical sphincters is rarely encountered in the other diseases of connective tissue. Although subjective joint complaints are not uncommon and flexion contractures occasionally occur, dermatomyositis can usually be differentiated from rheumatoid arthritis by the lack of objective evidence of inflammatory intra-articular disease. The most characteristic laboratory finding is the increased creatinuria which, although nonspecific, is greater than that found in the other diseases of this group.

Diffuse Scleroderma.—It is in the early stages, before skin changes are apparent, that scleroderma is most likely to be confused with rheumatoid arthritis. Not uncommonly scleroderma is associated with diffuse edema and puffiness of the fingers and hands, so that swelling, when present, is not confined to the periarticular region as it usually is in rheumatoid arthritis. Flexion deformities may develop. These usually occur without physical or x-ray evidence of intra-articular disease, in contrast to the situation in rheumatoid arthritis. When fully evolved, the skin changes of scleroderma are characteristic and not apt to be confused with skin involvement associated with rheumatoid arthritis. Raynaud's phenomenon and other evidences of vasomotor instability are sufficiently common in all of the disorders to be of no differential diagnostic value.

Pathology

It is most unfortunate that in an institution devoted to medical education no systematic examination of the articulations was undertaken in the course of postmortem examination of fifty patients with "diffuse collagen disease." Such an experience is not unique, however, and information regarding the histopathologic changes in the synovial tissue in these diseases is meager indeed. Limited information can be obtained by examination of the more readily accessible sternoclavicular joint or by punch biopsy of the synovial membrane of the knee. The accumulation of more precise information will require a constant effort to obtain permission for special examination of the articulations in these disorders whenever the opportunity presents itself.

Summary and Conclusions

1. In a review of fifty cases of connective tissue disease, in which the diagnosis was verified by necropsy, it was found that musculoskeletal manifestations occurred commonly and frequently resulted in confusion with rheumatoid arthritis or rheumatic fever.

2. Of twenty-one patients with systemic lupus erythematosus, musculoskeletal symptoms were the initial manifestation in eight (38 per cent). Musculoskeletal involvement was entirely subjective in seven (33 per cent), but was associated with objective joint findings in eleven (52 per cent). The clinical picture was confused with rheumatoid arthritis in five instances (24 per cent) and with rheumatic fever in six (29 per cent).

The correct diagnosis was usually suggested by one or more of the following: discrepancy between the severity or course of articular and extra-articular manifestations, erythematous eruptions of the face, serous membrane involvement with effusion, evidence of renal impairment, convulsions, toxic psychoses, clinical evidence of cardiac disease, false positive serologic tests for syphilis, leukopenia and presence of lupus erythematosus cells.

3. Musculoskeletal manifestations represented the mode of onset in four of eighteen patients with polyarteritis nodosa (22 per cent). Although such symptoms were noted at some time in ten cases (55 per cent), in only four (22 per cent) were objective joint findings described. These were confused with rheumatoid arthritis and rheumatic fever in two cases each.

The diagnosis of polyarteritis nodosa should be suspected when a patient with bronchial asthma develops eosinophilia in excess of 25 per cent or when a patient with hypertensive renal disease or apparent rheumatoid arthritis develops marked systemic or other symptoms not readily explained on the basis of the original diagnosis. The following signs and symptoms occurred with some frequency in this series and should also suggest the diagnosis: peripheral neuritis, abdominal pain, peptic ulcer, unexplained gastrointestinal bleeding, hypertension, nodular or necrotizing skin lesions, abnormal urinary findings, intermittent testicular pain, Loeffler's syndrome, x-ray evidence of diffuse granular disease of lung, persistent unexplained polymorphonuclear leukocytosis, or a recent history of serum sickness or reaction to sulfa drugs or penicillin.

4. Subjective musculoskeletal involvement occurred in three of five patients with dermatomyositis (60 per cent). Although flexion contractures developed in two, differentiation from rheumatoid arthritis was possible because of the absence of the usual physical signs of inflammatory intra-articular disease. As the disease progressed in these patients, muscular atrophy and weakness eventually far exceeded that encountered in the other patients of this series.

5. All of six patients with diffuse scleroderma had musculoskeletal complaints; in five (83 per cent) these represented the mode of onset. Although some degree of flexion deformity developed in all cases, differentiation from rheumatoid arthritis was again made possible by lack of evidence of inflammatory joint involvement.

6. The possibility of one of the connective tissue diseases, and especially of systemic lupus erythematosus, should be considered in cases of apparent rheumatoid arthritis which are atypical or associated with multiple system involvement.

Newer Drugs Used in Neurology

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IN presenting the subject of "newer" drugs used in neurology, choice of material will have to depend somewhat upon an interpretation of the adjective "newer." It might be interesting but not very helpful or practical to discuss only the very recently tried drugs which are still experimental and not yet released for use; on the other hand, I do not wish to spend too much time discussing drugs whose action is known to all of you and with which you have all had experience. The ideal ones to discuss would be those very recently made available which are not too generally known as yet. In this discussion I must necessarily mention certain drugs which are fairly well known in order to compare them with the newer ones; I will try, however, to discuss the drugs most recently released, as well as some which are still experimental but will very shortly be available.

Ataractic or Tranquilizing Drugs

Because of the widespread interest in and publicity about them, I am going to start with a brief discussion of the so-called ataractic, or tranquilizing drugs. As you know, these are used more in the field of psychiatry than in neurology. The term "ataractic" or "ataraxic" was proposed by Dr. Howard Fabing and is derived from the Greek noun which means freedom from disturbance of mind or passion; he felt that the term tranquilizing was not quite correct.[1] There are a number of these drugs. In spite of their wide publicity they do have limited uses and different indications, and in general they are not immediate in action. Most of them have small or no effect on so-called normal segments of population (Table I).

There are two general groups of these drugs and the first and best known group consists of those that have been used primarily in the major psychiatric disorders, such as schizophrenia, acute mania, and disturbed states. The first of these drugs, of course, is reserpine, which, as you know, has a long and romantic history through its derivation from the snake-root plant *(Rauwolfia serpentina)*. It was first used clinically in modern medicine in the treatment of hypertension. It was then found to have a tranquilizing effect without too much sedative action, and was later found to be very helpful in many acute psychiatric conditions, bringing about some measure of relief in about 60 per cent; violent patients are controlled much more easily and disturbed patients are more manageable, but the drug certainly cannot be considered a cure.[2] Reserpine has also been found to be helpful in the treatment of Huntington's chorea, especially in the early cases, and not only are the abnormal movements somewhat less marked but the patients' mental reactions are better. One must bear in mind, however, that this drug does cause some depression in a large percentage of patients to whom it is given, and for that reason it must be given in a relatively small dose and the patients must be followed quite closely. We have found that some of our patients with Huntington's chorea have been improved as far as their movements are concerned, but have become extremely depressed and even suicidal while receiving reserpine.

TABLE I. ATARACTIC, OR TRANQUILIZING, DRUGS

1. For Use in Major Psychiatric Disorders
   Reserpine (Serpasil)
   (Rauwolfia serpentina)
   Chlorpromazine (Thorazine)
   Promazine Hydrochloride (Sparine)
   Azacyclonol (Frenquel)
2. For Use in Psychoneurotic Disorders
   Meprobamate (Miltown, Equanil)
   Atarax
   Suavitil

The second in this group is chlorpromazine, which was first developed for study as an antihistaminic drug by the French.[2] It was found to be of value, also, in the vomiting of pregnancy, psychogenic digestive disturbances, various pain syndromes, and in the major psychiatric disorders, and it, like reserpine, has been widely used for the treatment of agitated and excited psychiatric patients, bringing about definite improvement in their mental reactions but still achieving no specific cure. It is also used to potentiate the effect of narcotics and barbiturates, and to aid in withdrawal of such drugs. Like reserpine, it may cause

some depression, and it also occasionally produces an obstructive type of jaundice. Both chlorpromazine and reserpine have been observed to bring about a Parkinsonian-like picture in patients who are taking them. The rigidity and tremor, however, disappear when the drugs are withdrawn. Patients receiving chlorpromazine should also be watched carefully for possible blood changes.

About a year ago another related compound, Sparine, or promazine, became available, and this seems to show some promise to have action related to that of chlorpromazine. It has, however, been studied very briefly thus far.[3]

A fourth drug which belongs in the list of the ataraxics is azacyclonol, or Frenquel.[4] This drug has no effect whatever on normal individuals and it is not indicated for minor neurotic disturbances, but has proved quite helpful in acute schizophrenic and confusional states, especially in postoperative confusion, and it has been used with some degree of success in cases of delirium tremens and in senile confusions. This drug has not been as widely used as reserpine and chlorpromazine, and there has been some disagreement on the part of various investigators regarding its effectiveness.

The other group of the ataractic drugs includes those which have no value in the psychotic patient but which are of help in the treatment of the neurotic or psychoneurotic patient. The best known of these is meprobamate, which is available under the trade names Miltown and Equanil.[5] This, which is a derivative of mephenesin, has been widely used in the United States during the past year for the control of nervous tension or "jitteriness," along with various symptoms which are subjective accompaniments of the anxiety which all of us have experienced at one time or another. These include tension headache, palpitation, a globus sensation in the throat, air hunger, anorexia, psychogenic digestive disturbances, "butterflies" in the abdomen, urinary frequency, muscle tension, and tremor. Meprobamate is no cure-all for these symptoms, but it is worthy of a trial for the relief that it may bring. I am afraid that this drug is being used too widely and oftentimes in too large a dose. Most patients should not or cannot tolerate more than 400 milligrams twice daily. The drug may cause an excessive relaxation of the musculature, which the apprehensive patient may consider to be an alarming weakness, and occasionally dizziness, too. It is a little too early to assess the value of this drug critically, but it seems to be most helpful where the patient has good insight into his condition and realizes that his symptoms are of nervous origin and are produced by stress. In such individuals the relief of the somatic complaints of his anxiety by this drug may be quite helpful.

With the popularity of meprobamate, other related drugs have been introduced. The Belgians have been studying a compound called Atarax, which is now available in this country, and the Danes one known as Suavitil.[1] It is still too early to make any definite statement about either of these. While these latter drugs are said to be non-habit forming and are really not sedatives, tense, nervous individuals may develop a great deal of dependence upon them if used for long periods of time. They should only be given temporarily during periods of extreme stress, and should never be used indefinitely or in excessive doses. Obviously the feeling of equanimity, which Osler described so well, is something that we should all attempt to attain, but drug induced equanimity is not the answer. I am sure, however, that none of these is really potent enough to be called a "don't give a damn" pill, which some headline writer has called them.

Cerebral Stimulants

The above-mentioned drugs are of use in states of tension, excitement, confusion and mania, but are of no benefit in the depressed, melancholic patients or in states of hypersomnia. It has been well known during recent years that the various drugs of the amphetamine group, such as Benzedrine, Dexedrine, ephedrine, and Methedrine, are cerebral stimulants or mood elevators, or, in other words, euphorants or analeptics (Table II). They have been of some value in states of moderate depression, in relief of excessive fatigue, and in the treatment of narcolepsy. In some instances in which their stimulating effect causes undesirable symptoms such as palpitation and insomnia, they are combined with one of the barbiturates. Recently pipradol (Meratran) has been found to have a similar action as a mood elevator in de-

TABLE II. CEREBRAL STIMULANTS

Ephedrine, Amphetamine (Benzedrine), Dexedrine, Methedrine
Pipradol Hydrochloride (Meratran)
Methyl-phenidylacetate Hydrochloride (Ritalin)
Pentylenetetrazol (Metrazol)

pressed states and also as a stimulant in the treatment of narcolepsy.[6] Another related drug is Ritalin, which has a similar action and has been combined with either reserpine or chlorpromazine in the treatment of agitated depressions and in senile psychoses. It both abolishes the side effects of these depressing drugs and in itself acts as a cerebral stimulant.[7]

There is extensive literature which suggests that Metrazol has a somewhat similar action and that it is of special value in the treatment of senile and arteriosclerotic patients, in whom it is said to act as both a stimulant and a vasodilator; it has also been given combined with nicotinic acid for the latter purpose.[8] Studies carried out in state hospitals report improvement in the behavior and conduct of senile and arteriosclerotic patients, with lessening of confusion and agitation and improvement in memory and intellectual functions following the oral administration of Metrazol. We have been unable to duplicate this effect on our patients, however, but ours are mainly outpatients and are not as severely deteriorated. It is possible that the nursing care and supervision of the institutional patients who are given this medication is responsible for their apparent improvement.

Muscle Relaxants

The search for drugs to bring about muscular relaxation in spastic and related states has been fraught with difficulties (Table III). Curare and d-tubocurarine do cause such relaxation by raising

TABLE III. MUSCLE RELAXANTS

Curare; d-Tubocurarine Chloride
Gallamine Triethiodide (Flaxedil)
Decamethonium Bromide (Syncurine)
Succinylcholine Chloride (Anectine, Quelicin)
Mephenesin (Myanesin, Tolserol)
Zoxazolamine (Flexin)

the threshold of the motor end-plate to acetylcholine and thus preventing depolarization by this latter substance, and decamethonium and succinylcholine cause a persistent depolarization. Both of these drugs do produce muscular relaxation, but the limits of safety are such that they have to be used very carefully, and, furthermore, these preparations only act when given parenterally, and their action is very brief. Another drug, mephenesin, or Tolserol, also causes some muscular relaxation; this, however, is not by its peripheral action, but because it causes central depression of polysynaptic neural pathways by blocking internuncial motor neuron discharges.[9] This drug, too, is most effective when given parenterally, and its action when given orally is less than it was once thought to be; consequently, it has not proved to be very effective in states of marked spasticity. A new drug, zoxazolamine (Flexin), which is related to mephenesin in its effect on polysynaptic neural transmission, has been of more value than previously used drugs in the treatment of spasticity of various types.[10] This, given in doses of 250 to 500 milligrams three to four times a day, has been used in the treatment of the increase in tone associated with cerebral lesions, including hemiplegia, Parkinsonism, cerebral palsy, spastic paraplegia, and multiple sclerosis. Our own experience with this drug has shown it to be a moderately effective therapeutic agent in the treatment of spasticity, and it has been most helpful in cases of spasticity or spinal cord origin.[11] Its action is similar to that of mephenesin, but somewhat longer, and it is more potent. It is of interest that both mephensin and Flexin have been shown to decrease the electroencephlographic abnormality of petit mal epilepsy, but thus far neither of these has been found to be of definite therapeutic value in this condition.

Drugs Used in Myasthenia Gravis

Two new drugs have recently become available in the treatment of myasthenia gravis, as well as one new drug for the diagnosis of this condition (Table IV). During recent years neostigmine has,

TABLE IV. DRUGS USED IN MYASTHENIA GRAVIS

Pyridostigmine Bromide (Mestinon)
Ambenonium Chloride (Mysuran)
Edrophonium Chloride (Tensilon)

of course, been the standard drug for both diagnosis and treatment. It does, however, have a very brief action. It has to be taken frequently in patients with severe involvement, and they have a definite "let down" when the effect of the drug is worn off. In the attempt to find a longer acting preparation, the various organic phosphates were tried, but their potential toxicity is such that they were never universally accepted. A year or two ago a homologue of neostigmine, pyridostigmine, or Mestinon, became available.[12] This drug, which is only about one-half as potent as neostigmine, has a much more prolonged action, and patients do not note the "let down" when its effect is worn off. It is noteworthy that not only does Mestinon

have a more prolonged effect than neostigmine, with more even maintenance of strength, but it also has less toxicity and is much less apt to cause muscarinic effects.

Another new drug used in treatment of myasthenia gravis is ambenonium chloride, or Mysuran, whose anticholinesterase properties are from five to ten times that of neostigmine.[31] It also has a much more prolonged action than either neostigmine or Mestinon, but its toxic effects are somewhat between the two, and it may cause both parasympathetic overactivity and central nervous system stimulation. Its action is so prolonged that few patients need more than three to four tablets a day, and many of those receiving this new drug have no longer need to take medication before breakfast if taken before retiring at night. Because of its slow action the drug must be taken regularly, and patients cannot afford to let themselves "run down," since it takes too long for the next dose to "pick them up again." Both of these drugs are definite advances in the treatment of myasthenia gravis.

Edrophonium chloride, or Tensilon, has a direct action on the neuromuscular junction and has both anticurare and anticholinesterase effects. It has such a brief action that it is not of much value in the treatment of myasthenia gravis, but it has been shown to be a very effective drug in the diagnosis of this condition.[14] One cubic centimeter (10 milligrams) injected intravenously in the patient with myasthenia gravis is followed by improvement in the strength of the weak muscles within thirty seconds, and this increases to its maximum within one to ten minutes. The action, however, is very brief; strength begins to decline after ten minutes, and the total effect of the drug lasts less than an hour. Actually Tensilon does not give any definite improvement over the older diagnostic test with the use of neostigmine methylsulphate, but it affords a quicker test, and may be of value in certain patients who may for some reason or other fail to respond to neostigmine.

Drugs Used in Epilepsy

There has been a constant attempt during the past twenty years to find more effective drugs in the treatment of epilepsy (Table V). Actually, the drugs that are in standard use at the present time for the grand mal or major seizures are quite effective. These are the barbiturates, principally phenobarbital, Mebaral and Gemonil, and the hydantoinates, namely Dilantin and Mesantoin. Because the former drugs all have some sedative and hypnotic effects, and the latter ones may produce side effects or toxic reactions, there have been attempts to synthesize related compounds. Many of the hydantoinates that have been used experimentally, however, as well as a few that were on the market temporarily, had a potential toxic effect on the blood-forming system, and consequently they are no longer used. One of the two that I have mentioned, Mesantoin, does to a certain extent have such potential effects as well, but in many patients it may be substituted for Dilantin if the latter drug is not effective or cannot be tolerated. There is one additional hydantoinate, Peganone, which is 3-ethyl, 5-phenyl hydantoin. This seems to produce few side effects; it does not cause the gingival hypertrophy that not infrequently develops in children who use Dilantin, and thus far at least no blood changes have been reported.[15] It is less potent than Dilantin and has to be given in a somewhat larger dose, and possibly 500 milligrams three times a day may be necessary to replace 100 milligrams of Dilantin three times a day. This drug is still an experimental one, but it has been investigated quite widely, and will undoubtedly be released for general use rather soon.

TABLE V. DRUGS USED IN EPILEPSY

Peganone (3-ethyl, 5-phenyl hydantoin)
Primidone (Mysoline)
Methylphenylsuccinimide (Milontin)
Acetazolamide (Diamox)

Primidone (Mysoline) has been used quite extensively during the past few years.[16] It is said to be effective in both grand mal and psychomotor seizures, although experience shows that it is not quite as effective in the former as Dilantin nor in the latter as Phenurone, although it is less toxic than Phenurone. It apparently has no serious toxic effects, but it may cause drowsiness, gastrointestinal symptoms, ataxia, and, in a few patients, delusions. It is certainly a drug that can be tried in cases where the more usual ones prove unsatisfactory.

If one uses the long-accepted clinical classification of epilepsy as to the grand mal, petit mal, and psychomotor varieties, it is the latter two that have been the most difficult to control by drug therapy. Phenurone, which cannot be considered a new drug and which some people hesitate to use be-

cause of its toxic potentialities, and possibly Mysoline, are the principal drugs that seem to have some specific action in the psychomotor seizures. The drugs of the dione group, namely Tridione (Trimethadione) and Paradione (Paramethadione) were the most effective drugs up until a year or two ago, and possibly still are the most effective ones, for petit mal seizures. Tridione seems to be more helpful than Paradione, but it is potentially more toxic, especially on the bone marrow. A few years ago an entirely different form of pharamacologic preparation, methylphenylsuccinimide (Milontin), was brought out for the treatment of petit mal seizures, and is undoubtedly a helpful drug, although we have not been too enthusiastic about its effectiveness in our clinic, and have been interested in seeing that the later reports are less optimistic than the original ones.[17] It must be given in a rather large dose, but its toxic effects are minimal.

It has recently been brought out that acetazolamide (Diamox), a carbonic anhydrase inhibitor, which was originally used as a diuretic in the treatment of congestive heart failure, had anticonvulsive properties and seemed to be especially effective in the treatment of petit mal epilepsy.[18] At one time it was felt that this drug, which causes profound metabolic changes and affects the acid-base balance of the blood and body fluids, might act in a way similar to the ketogenic diet which was once advocated for petit mal epilepsy. It has been observed, however, that the beneficial effects are not clearly correlated with either the dosage of the drug or the level of the carbonic antihydrase activity in the blood and, therefore, it has been suggested that it may act directly on the metabolism of the cerebral neurons.[19] Some authorities have suggested that Diamox may be helpful in all types of epilepsy, and in one report evidence is brought forth that the patient who stands the best chance of being helped by it is the one whose electroencephalogram not only exhibits a spike-wave dysrhythmia but also displays prompt response to the alkalosis caused by overventilation. Although there have been some rather enthusiastic reports on this action of Diamox, our own results seem to show that it is not of value when used alone. We have observed a few patients in whom the addition of the Diamox to the previous anticonvulsant therapy seemed to bring about a definite lessening of the frequency of the seizures. Diamox is a sulfonamide derivative, and it is of interest that a case of fatal bone marrow depression after its use was recently reported.[20] I would state that its use is limited, but it is perhaps worth considering as an adjuvant to more established pharmacologic agents.

Some of the cerebral depressants and tranquilizers as well as some of the muscle relaxants have been used in epilepsy. It is believed that certain types of seizures, principally those of the petit mal variety, are of deep level origin; Penfield refers to them as "centrencephalic." It is probable that reserpine, chlorpromazine, mephenesin, zoxazolamine and meprobamate, all act on the upper brain stem and lower diencephalon, and one might expect them to be effective in certain types of epilepsy, or at least to have a potentiating action. It has been observed that both mephenesin and zoxazolamine may depress the petit mal wave pattern in the electroencephalogram, and there have been statements that the latter drug, as well as meprobamate, has been of value in the treatment of petit mal epilepsy.[21] However, while these drugs probably do inhibit the excessive spread of impulses in the subcortical brain masses, they have not as yet shown to be of practical value in the treatment of epilepsy.

Drugs Used in the Treatment of Parkinsonism

There have been many drugs brought out during recent years which have been advocated for the relief of the rigidity and tremor of Parkinson's disease and related conditions. Most of them are synthetic drugs with an atropine-like effect, and they are also related to certain of the antihistamines. A list of a few of these is shown in Table VI. On the basis of our own experience, I would say that Artane and Pagitane are the most effective of the group and the least apt to be accompanied by side effects or toxic reactions.[22] With all, however, there may be side effects similar to those which accompany the use of atropine or hyoscine, namely, dry mouth, blurred vision, nausea, and dizziness, and their use in the elderly is

TABLE VI. DRUGS USED IN PARKINSONISM

Trihexyphenidyl (Artane)
Caramiphen (Panparnit)
Cycrimine (Pagitane)
Benztropine (Cogentin)
Ethopropazine (Parsidol)
Procyclidine Hydrochloride (Kemadrin)

sometimes followed by mental confusion and retention of urine. Inasmuch as the patient with Parkinsonism may show a varying response to drugs, it is often worth while to try more than one of these, either alone or in combination, or with one of the antihistamines, usually Benadryl or Thephorin. It should be borne in mind that when any of these "newer" synthetic drugs is used, the dosage should be built up very slowly; by doing this it may be possible to avoid side effects on toxic reactions.

Miscellaneous Drugs

There are many other new drugs that are of interest in neurology, but their range of use is limited and I shall just mention a few briefly in passing (Table VII). The treatment of lead poisoning, both lead encephalopathy in infants and

TABLE VII. MISCELLANEOUS DRUGS

Edathamil Calcium-Disodium (Calcium Disodium Versenate)—Lead Poisoning
Dimercaprol (BAL)—Wilson's Disease and Heavy Metal Intoxications
Procaine Amide—Myotonia Congenita and Dystrophica
Cortisone and Corticotropin (ACTH)—Acute Exacerbations of Multiple Sclerosis (especially ocular), Polymyositis, Guillain-Barré Syndrome

lead neuritis in adults, has changed radically during recent years. The chelating agents have been used in industry for some time, but it has been found fairly recently that they are of value in various intoxications in man, and Edathamil, or calcium disodium versenate, is now an important tool in the treatment of lead poisoning and some other heavy metal poisonings.[23]

Dimercaprol (BAL) has been used for some time in the treatment of heavy metal poisonings, especially those associated with ingestion of or exposure to arsenic, gold, mercury, and possibly lead. It has fairly recently been shown that Wilson's disease, or hepatolenticular degeneration, is associated with a disturbance of copper metabolism in the body, and there have been some reports of the relief of the symptoms of Wilson's disease by the use of Dimercaprol.[24] More recently the versenates, too, have been used in the treatment of Wilson's disease. It is too early to know how effective either of these agents will be, however, and from our limited experience with them, we do not have the enthusiasm that has been reported elsewhere in the literature.

Another drug that might be mentioned briefly in passing is procaine amide, which has recently been advocated in the treatment of myotonia dystrophica.[25] Quinine has been shown to be of some value in relieving the myotonic manifestations of this disease, and of myotonia congenita as well, but it must be given in rather large doses and many patients are unable to tolerate such administration because of the development of cinchonism. Procaine amide seems to relieve the prolonged muscular contractions that are a part of this disease, and therefore to diminish to a certain extent the motor disability. It is doubtful, however, that it in any way prevents the gradual progression of this disease.

Cortisone and corticotropin (ACTH), which are used so widely in medicine in general, do, of course, have their place in neurologic therapy also, but it must be stated that there are very few disorders of the nervous system in which they are of proved specific therapeutic value. They are used frequently for exacerbations of multiple sclerosis, but seem to be most effective in those exacerbations characterized by ocular difficulties, mainly retrobulbar neuritis and acute optic neuritis. Even in these it is difficult to assess their effectiveness, as these sometimes are self-limited. They are also used in the neurologic manifestations of collagen diseases, principally periarteritis nodosa and disseminated lupus, and most specifically in the condition known as polymyositis, which is being diagnosed more frequently at the present time and is sometimes mistaken for a rather rapidly progressive myopathy or dystrophy. They are also used fairly regularly, and probably of value, in the treatment of the Guillain-Barré syndrome, or polyradiculoneuritis, and have been said to be of value in the immediate therapy of apoplectic strokes, but this latter has not been confirmed.

Anticoagulant Therapy in Cerebrovascular Disease

I would be remiss in this discussion of "Newer Drugs in Neurology" if I did not make some mention of the recent interest, or possibly renaissance of interest, in the use of anticoagulant drugs in cerebrovascular disease. The widespread incidence and poor prognosis in cerebrovascular disease has always been a matter of concern to the neurologist and the physician in general, but specific modes of therapy have not been available. It has been especially important to try to find some specific method of treating the acute cerebral

infarct which is secondary to either thrombosis or embolism of one of the major cerebral vessels. Vasodilators of various types have been widely used, but there is little clinical evidence and no experimental evidence that any of them causes actual dilatation of the cerebral vessels. Experimentally, inhalations of carbon dioxide do cause cerebrovascular dilatation, but they likewise reduce the blood flow and have not proved to be of very much therapeutic value. Cortisone, as was just stated, has also been advocated in acute strokes, but its effectiveness, too, is doubtful.[26] A few years ago there was a great deal of enthusiasm for stellate ganglion block in cerebral thrombosis and embolism, but this enthusiasm has fast faded.[27] While there are still a few physicians who advocate this procedure and who report definite benefit, by far the majority who have studied their cases closely feel that the procedure is not of real help, and experimentally, too, there is no evidence that a cervical sympathetic block dilates the cerebral vessels, or especially that it dilates those vessels which are occluded by either a thrombosis or an embolism, or that it in any way increases the blood supply in an infarct resulting from such obstruction.

TABLE VIII. CURRENT INDICATIONS FOR ANTICOAGULANT THERAPY IN CEREBROVASCULAR DISEASE

Intermittent Insufficiency of Basilar Arterial System
Thrombosis within the Basilar Arterial System
Intermittent Insufficiency of Internal Carotid System
Thrombosis of Internal Carotid Artery
Recurrent Thromboembolic Episodes of Cardiac Origin

Theoretically at least, anticoagulant drugs such as Heparin and Dicumarol might be of value in cerebrovascular occlusions as they are in occlusions of the coronary arteries.[28] They have been used hesitatingly, however, because it has always been feared that the infarct secondary to the occlusion may be a red, or hemorrhagic, one rather than a white, or anemic, one, and the use of anticoagulants in the presence of the hemorrhagic infarct may cause further bleeding and therefore cause a worsening rather than an improvement in the patient's condition. It has recently been advocated, however, that anticoagulant therapy is of value in certain types of cerebrovascular disease (Table VIII). These are the following: intermittent insufficiency within the basilar arterial system or actual thrombosis of the basilar artery or one of its branches; intermittent insufficiency within the internal carotid arterial system or actual thrombosis of one of the internal carotid arteries; and recurrent thromboembolic episodes of cardiac origin, that is, secondary to subacute bacterial endocarditis, vegetative heart disease, or heart disease associated with auricular fibrillation.[29] In each case, the general contraindications to anticoagulant therapy, both absolute and relative, must be considered. Careful diagnosis of a particular type of cerebrovascular involvement is essential, and one must be certain that the vascular disease is either thrombotic or embolic and not hemorrhagic. The immediate and late course of the patient must be followed carefully, with frequent determinations of the prothrombin time. There is definite evidence, however, from centers where this has been carried out on fairly large series of patients and from our own brief but, we think, careful studies on a small number of patients, that the use of anticoagulants is of definite therapeutic value in certain patients with cerebrovascular disease, especially of the types I have mentioned. Furthermore, there is evidence to suggest that this technique is of prophylactic value and decreases the incidence of recurring episodes of either thrombotic or embolic origin.

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Sudden Unexpected Death

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SUDDEN unexpected death is no rarity. According to our late medico-legal expert Louis Regan,[1] 15 to 20 per cent of all deaths in the U. S. result from violence or occur unexpectedly from obscure causes. About one murder each year for every 10,000 living persons is officially recognized. Interest in and prevention of this type of sudden unexpected death concern judicial and law enforcing agencies and, to a degree, also psychiatrists. We are interested today in cases which occur without an evident extrinsic etiologic factor and whose pathogenesis may or may not be satisfactorily explained at autopsy. Let us first review a few instances of the first category, that is, cases of sudden unexpected death with clinical explanation and autoptic confirmation.

If we use the term "unexpected" we have to realize that there are different grades of unexpectedness. It may be absolute or only relative with regard to the time of the sudden death. If an apparently healthy person drops dead without premonitory symptoms of coronary disease, then his sudden death due to coronary occlusion was absolutely unexpected. If a person had had one or several attacks of myocardial infarction previously, or if he had been known to suffer from coronary insufficiency, his sudden death was unexpected only at the time of his sudden death; it could have been expected, however, at any time.

Some thirty-five years ago I was taking the history of a man in his fifties with symptoms of gallbladder disease. When I started the physical examination, he suddenly collapsed, lost consciousness and died within the next hour of a cerebral hemorrhage. This was absolutely unexpected. If I had known previously that the man had atherosclerosis and hypertension his death would have only been relatively unexpected. The sudden death from subarachnoid hemorrhage of one of Harvard's most outstanding clinicians some years ago was absolutely unexpected. Sudden death from a ruptured, previoulsy known aortic aneurysm can be foreseen but may occur at any time unexpectedly.

Similar situations of a relatively unexpected sudden death are numerous. I mention only pulmonary embolism due to a fibrillating heart or in phlebothrombosis, which may develop and escape our attention after surgical procedures or after delivery. Allergy is always a potential danger. Yet anaphylactic shock following injection of corticotropin is absolutely unexpected, especially after it had been injected twice before to combat asthma of the same patient. Capillary congestion and hemorrhages in lungs, kidneys and adrenals showed that the sudden unexpected death actually was due to anaphylaxis.[2] Sudden death during quinidine therapy is not particularly rare. Restoration of rhythmic atrial contractions may lead to embolization by mural thrombi which had developed during the preceding time of atrial fibrillation. This type of sudden death, however, had been confirmed only once in ten autopsied cases. In the nine other instances, it had to be interpreted as "quinidine shock," with circulatory collapse and respiratory paralysis.[3]

At one of my ward rounds, the resident presented a young woman with presumptive diagnosis of hysteria. She complained only of intense dizziness on changing her position, and physical examination had been completely negative. My suspicion of a cyst in the fourth ventricle suggested by the definite dependence of dizziness on change of position was confirmed by a sudden (relatively) unexpected death on the following day. The cyst was found on autopsy.

Sudden death by suicide may be absolutely unexpected in a healthy person, apparently normal mentally; it would be only relatively unexpected as to the time of its commitment if the person had been suffering from an incurable disease or from severe mental depression. Although suicide represents sudden death by an extrinsic force, it is an intrinsic mental factor that puts this force into action.

Sudden unexpected death is known to occur in athletes after extraordinary exertion. The most famous instance is the case of the Greek Marathon runner who dropped dead after having delivered his message. Such cases of sudden fatal heart

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failure apparently are brought about by a mechanism elucidated by Raab.[4] He found excessive amounts of epinephrine-like substances in the heart muscle of a young athlete, and believed that acute poisoning with epinephrine-sympathin-norepinephrine accounted for ventricular fibrillation and sudden death. The great importance of the constitutional factor in such rare events is well illustrated by the sudden death of identical twins who were outstanding athletes.[5] One of the brothers was autopsied and was found to have a hyperplastic thymus and narrowness of the descending aorta. Furthermore, he had coronary arteriosclerosis and hydronephrosis affecting the left kidney. As a matter of fact, coronary arteriosclerosis with subsequent thrombosis may cause an unexpected sudden death even in young individuals.

Hypoplasia of the coronary artery and of the musculature of the left ventricle was found after the sudden death of a thirty-six-year-old woman who had been suffering from attacks of paroxysmal ventricular tachycardia with Adams-Stokes syndrome.[6] Unexpected sudden death without anatomic findings except for hypoplasia of the aorta occasionally has been reported in the past.[7]

Sudden unexpected death is a threat to which carriers of sickle-cell hemoglobin are exposed. Whether these persons, almost exclusively of the Negro race, carry only small amounts of the abnormal S-hemoglobin and may have been asymptomatic and healthy with the sickle-cell trait (sicklemia) only, or whether they had been suffering from sickle-cell anemia since childhood, sudden unexpected death may terminate their life prematurely by vascular occlusion and thromboses or by hemorrhages in vital organs.[8]

So far, we have spoken of instances of sudden unexpected death that present no great riddle at autopsy. The pathologist is able to demonstrate the presumptive cause of death and to confirm the interpretation offered by the clinician. The problem of sickle-cell disease, however, leads us also to the second category of sudden unexpected death which remains unexplained at autopsy. The pathologist may or may not register some abnormal findings concerning the morphology of the dead person; he fails, however, to offer a satisfactory explanation of the pathogenesis of such death. A functional disturbance must have been responsible, the elucidation of which can only be the job of the clinician, not of the pathologist.

Cases of this kind have attracted the attention of the medical profession and, of course, particularly of legal medicine for a long time. In the past era of overwhelming preponderance of pathologic anatomy, as contrasted with pathologic physiology, it might have been understandable that certain unusual anatomical findings at autopsy could be proclaimed and accepted as at least legally sufficient explanation of cases of sudden unexpected death, although the relationship of those findings to the pathogenesis of death remained obscure. Status thymicus, status lymphaticus and thymolymphaticus (A. Paltauf 1889), and, some twenty years later, status hypoplasticus (Bartel) served as scapegoats to preserve the supremacy of pathologic anatomy. Experiences of the first World War, however, taught a different story. Sudden death without previous disease due to extrinsic causes of warfare prevents the very rapid involution of the normal thymus and lymphatic apparatus brought about by any fatal disease. What had been considered as status thymicus and lymphaticus before, became recognized as normal findings in persons who died suddenly by violence, not by disease. There are, to be sure, rare cases of actually hyperplastic thymus and hyperplastic lymphatic tissue, but these morphologic findings do not help us to understand the proclivity of their carriers to sudden unexpected death. Nor do morphologic findings, such as hypoplasia of the aorta or the adrenals and developmental defects of various organs *per se*, contribute to our understanding.

And yet, it is apparently not pure coincidence if such anatomical findings can be observed more frequently in persons who died suddenly and unexpectedly without autoptic explanation of their death. Similar findings of developmental defects and aberrations are not uncommon in carriers of sickle-cell hemoglobin.[9] This is why sickle-cell disease, with its propensity to sudden unexpected death, may occasionally also fall into this second category, lying beyond the competence of the pathologist. It has been common experience that carriers of sickle-cell hemoglobin are what we call poor medical and surgical risks. To understand the pathogenetic mechanism involved in this category requires a much broader biologic viewpoint.

Sickle-cell hemoglobin is a hereditary, that is, genetic, deviation from the norm. It is an abnormal constitutional trait, and, as such, often associated with other abnormal constitutional characteristics. Sickle-cell disease is often not merely a

single genopathy but a polygenopathy—a multiple, genetic aberration from that average genetic type in man which represents the best adjustment to his environment so far achieved by biologic selection. Marked deviations from this state may involve diminished adjustment, lowered resistance, greater morbidity, and often predisposition to unusual disease processes emerging from the abnormal or defective genes.[10]

This concept is the clinical application of a general biologic law first recognized by Tom H. Morgan, the greatest American geneticist. Single genes usually have multiple effects which is known as pleiotropism of genes. One abnormal gene which may be recognized as a trifling and apparently *per se* insignificant deviation from the norm of a superficial character may affect the viability and vitality of the whole organism. This biologic law must be referred to, in my opinion, in order to understand the frequent findings of various developmental defects, malformations, and hypoplasias at the autopsy of persons who had been victims of sudden unexpected death, which remained unexplained with the tools of pathologic anatomy. In a recent study on unexpected death in early life Arey and Sotos[11] found eighteen cases with various malformations, particularly, but not exclusively, of the circulatory system, such as septum defect, Fallot's anomaly, abnormal pulmonary venous return, mongolism, and others. In spite of these autoptic findings, the mechanism of the unexpected death was not clear. I subscribe to the conclusion of the authors who recommend omitting the term "status thymolymphaticus" from medical writings, however, only with the reservation that it is meant to serve as explanation of sudden unexpected death.

What, then, is the explanation offered by pathologic physiology? There can hardly be any question that sudden unexpected death of this, our second category, that remains unexplained at autopsy, must be caused by arrest of the heart action. This can be an actual asystole—cardiac standstill—or ventricular fibrillation. What can bring about such an event? Excessive stimulation of the vagus nerve has been known to arrest the heart action under certain circumstances. A blow to the solar plexus or the testes, pressure on the carotid sinus or sudden dilatation of the rectum may be immediately fatal by a reflex action on the vagus. Cardiac arrest was recently reported due to traction-reflex from the stomach, occurring twice on the same patient during gastrectomy for carcinoma of the pylorus.[12]

Stimulation of the cardiac sympathetic nerves augments the amount of norepinephrine in the heart muscle of experimental animals, and injected norepinephrine, and even more so, epinephrine are eagerly absorbed by the heart muscle and stored in an active form in large quantities. These findings of Raab[13] corroborate his previously-mentioned explanation of sudden unexpected death by ventricular fibrillation of athletes after excessive physical exertion.

Exaggerated irritability of the intracardiac conduction system, with potential establishment of disorderly discharging foci, may occasionally account for anatomically unexplained fatalities. Sudden unexpected death in the course of an attack of paroxysmal tachycardia is rare.[14] If cardiac arrest occurs in an apparently perfectly healthy person with an asymptomatic Wolff-Parkinson-White syndrome, it is certainly absolutely unexpected and anatomically unexplained.[15]

It is conceivable that a severe blow to the autonomic centers may become acutely fatal whether it comes from outside or inside. An electric current passing through these centers may be such an outside blow and account for a sudden, relatively unexpected, death, a risk that is involved in the administration of electroshock therapy.[16] A blow, that is, intense stimulation of the vagal or cardioaccelerator centers or both, may occasionally occur from inside. The autonomic nervous system is a mediator between the emotional and somatic sphere of an individual. It is the legitimate transmitter of emotions into somatic manifestations. These may be vasomotor, secretory, visceromotor, and, particularly, cardiomotor in type. In rare cases, a fatal catastrophe due to cardiac arrest is a possibility if the emotional impact is exceptionally heavy and the responsitivity of the autonomic centers, and that of their most vital target organ —the heart, is excessive.

It stands to reason that highstrung, nervous, hypersensitive individuals, or those with damaged hearts, have a greater chance than do calm, emotionally-balanced persons, to suddenly succumb to an overwhelming emotional impact,[17] be it acute or of long standing. An example of this latter type is the sudden death under voodoo influence in primitive, uncivilized populations. Anxiety states due to belief in sorcery and magic used by one's adversaries have recently been reported as an

almost "normal component of the sociocultural situation in Nigeria."[18] Pathologic exaggeration of such a perpetual state of mind, not hampered by reasoning, is well known as a not uncommon cause of death. This form of death from magic and auto-suggestion, without any demonstrable pathologic cause, has even been called "thanatomania" (Ackerknecht).[18]

Similar to voodoo influence in man is death of rats under restraint or in situations in which they are helpless.[19] Timid, wild rabbits with highly labile autonomic nervous systems may develop typical hyperthyroidism if exposed to fright situations. Capture alone may elicit severe shock and even sudden death.[20]

"Death from broken heart" although always regarded with utmost skepticism, could never have been rejected as a possibility. Cases of sudden unexpected, and anatomically unexplained, death after an emotional shock, after slight physical punishment accompanied by hostile resentment and sense of humiliation, or in a state of great fright, have been occasionally reported.[7] Such a case was, for instance, a soldier who dropped dead after having been slapped in the face by a sergeant in the old Austrian army. I saw a middle-aged, extremely apprehensive woman die suddenly in the waiting room of the nose and and throat department in Vienna before she had been led into the operating room for an ambulatory minor operation of the nose. The autopsy revealed nothing to elucidate the case. Similar instances have been observed in several members of a family, which induced French authors to speak of a "diathèse de mort subite." The following observation, made in the Los Angeles County Hospital two years ago, illustrates well how sudden unexpected death may result from an overwhelming emotional storm.

Case Report

A twenty-seven-year-old, intelligent Negro girl from Arkansas had been suffering from occasional asthmatic attacks since the age of three years, often occurring with upper respiratory infections. At the age of seventeen, in 1945, she delivered an illegitimate baby. Since the time of pregnancy the asthmatic attacks became more frequent and severe. She left her home town and moved to California. In Los Angeles she was treated in the outpatient clinic of the County General Hospital. Several times she had to be admitted to the medical service for treatment of severe episodes. The allergy clinic found her to be sensitive to house dust and grass. Physical examination of the patient never revealed anything abormal except the typical wheezing respiration, prolonged expiration, and the characteristic rhonchi during attacks. Routine laboratory examinations were likewise negative. There were 4 per cent eosinophils among 6,700 white blood corpuscles. She responded to the usual treatment but needed epinephrine with increasing frequency. Her behavior, however, left hardly any doubt that a great deal of psychogenic overlay was an important pathogenetic factor. She was suspicious of everyone and kept asking the doctors if they thought she was crazy. She was extremely religious and her brother stated that she had frequent dreams about God and that she wanted to go to the hospital to die. Twice she had been advised to consult the psychiatric clinic but she failed to keep her appointment.

It was obvious that a deep psychogenic element was involved in the pathogenesis of her asthma and that psychiatric inquiry was imperative. The intern, Dr. Harry Roth, in charge of her case, first tried in vain to gain the patient's co-operation, but finally he succeeded. We shall re-enact this scene as it actually took place, from the very accurate notes of Dr. Roth. It should be emphasized that the patient showed no evidence of asthma before and during the interview.

The most dramatic events that followed cannot be re-enacted. The patient lost consciousness, had a generalized tonic seizure, and within two minutes respiration stopped and there was no pulse or blood pressure. Artificial respiration was instituted immediately, and the airways appeared to be free. Vasoxyl, caffein, and, intracardially, epinephrine were administered without success. After a few minutes Dr. Roth took a heroic step and performed a thoracotomy on the ward in order to institute cardiac massage. The heart showed no fibrillation. Continuation of cardiac massage for several minutes did not revive the patient. The tragedy was closed.

Unfortunately, an autopsy was not done because the family refused to give permission. What, then, caused the sudden unexpected death of this patient? She had no asthmatic fit preceding her death, there was no evidence of heart disease or embolism or of a cerebral accident, and there was no ventricular fibrillation. She died from cardiac standstill which occurred during a tremendous emotional turmoil when the patient had ventilated her carefully hidden secrets for the first time. There can hardly be any doubt that the interview, not the asthma, had been the killer. Not the disease—bronchial asthma—but rather the personality behind the disease, with its constitutional background and life experiences, proved to be the actual lethal factor. The interview acted as the trigger.

Summary

1. Sudden unexpected death without evidence of an extrinsic etiologic factor occurs frequently, and, in the great majority of cases, can be explained clinically and the explanation confirmed at autopsy.

2. Unexpectedness of sudden death may be absolute or only relative—with regard to the time of the sudden death. Relatively unexpected sudden death may occur, for instance, in a person with known coronary artery disease, aneurysm, phlebothrombosis, severe allergy, and sickle-cell disease.

3. There are infrequent instances of unexpected sudden death that remain unexplained at autopsy and can be understood only as result of disturbed function rather than altered structure.

4. Autopsy may or may not reveal abnormal findings concerning the morphology of the dead person, which fail, however, to offer a satisfactory explanation of the etiology and pathogenesis of the sudden unexpected death. Status thymicus, lymphaticus or hypoplasticus with hypoplasia of the aorta or adrenals, and various developmental malformations are such findings.

5. Sudden unexpected death must have occurred as result of cardiac arrest with or without preceding ventricular fibrillation. Excessive stimulation of the vagus nerve or cardiac sympathetic nerves and excessive irritability and responsivity of the heart as their target organ may bring this about. The abnormal individual propensity to cardiac arrest without cardiac disease may be linked with various morphologic developmental abnormalities on a genetic basis.

6. Severe blow to the autonomic nervous centers may derive from an intense emotional disturbance or acute shock. Cases of sudden unexpected death due to this pathogenetic mechanism are well known (voodoo—in primitive, uncivilized populations, captured timid wild rabbits, etc.).

7. The case of an unexpected sudden death during a psychiatric interview of a twenty-seven-year-old girl with bronchial asthma has been reported in some detail.

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The Growth and Development of Mentally Retarded Children

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THE State of Michigan is experiencing a severe strain on its available facilities for mentally retarded children. With a view toward helping the situation, the University of Michigan has inaugurated a longitudinal study of the growth and development of severely retarded children. The first two years of the study are being financed by an allocation from the special appropriation from the Michigan Legislature for Research and Service in the Utilization of Human Resources. The over-all purpose of the study is to provide a basis for improved educational programs for severely retarded children.

During the 1956-57 school year data were collected on the physical, mental and social growth of 103 severely retarded children and the causes for their retarded condition. This paper will summarize the data and make suggestions regarding the importance of the findings for legislators, teachers, parents and others who are concerned with the care and education of retarded children.

Setting and Subjects of the Study

The subjects of the study attend the Coleman School, Inc., in Detroit. The Coleman School accepts children between the ages of five and eighteen years who have been excluded from regular or special classes in their own school districts in the Metropolitan Detroit Area. In general the pupils at the school are not retarded to the extent of needing custodial institutional care. This is the type child whose social and educational needs have been discussed frequently throughout Michigan during recent years.

Physical Growth of Retarded Children

Data from this study show that, when compared with brighter children of the same age, the children who make up the sample are shorter and weaker. At twelve years of age the average height age of children at the Coleman School is a full year less than the average height age of children enrolled in the University School at Ann Arbor. The deficiency in muscular development, as measured by strength of wrist grip, is much greater than the deficiency in height. The average grip strength age of the retarded children at the Coleman School is four years less than the average grip strength age of children of the same age at the University School.

The importance of the physical development of retarded children is frequently overlooked by parents, teachers, and others. The lack of physical size and muscular strength is frequently accompanied by poor motor co-ordination. The combination gives an immediate impression of inadequacy and places retarded children at a distinct disadvantage with both adults and children. This disadvantage is increased when a lack of intelligence becomes more obvious. At five years, the proper age for school entrance, the retarded child looks and behaves physically like a child of three or four. It is no wonder that a prediction of no learning and a feeling of despair comes so easily to those who face the problem of caring for and teaching children who are obviously so lacking in the basic characteristics of average and bright children.

Mental Growth of Mentally Retarded Children

The idea that most retarded children enjoy some mental growth may come as a surprise to many persons. Figure 1 shows the superiority in mental development of the older subjects of this study. Figure 1 also shows that individual differences in mental age increase with chronological age. This is precisely what happens among brighter children. The constant increase in individual differences has not been generally recognized among retarded children. As a result, the brighter children among the retarded have gone

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unrecognized because they are viewed as part of a homogeneous group which cannot learn.

The evidence of mental growth among the subjects of this study seems worthy of straightforward

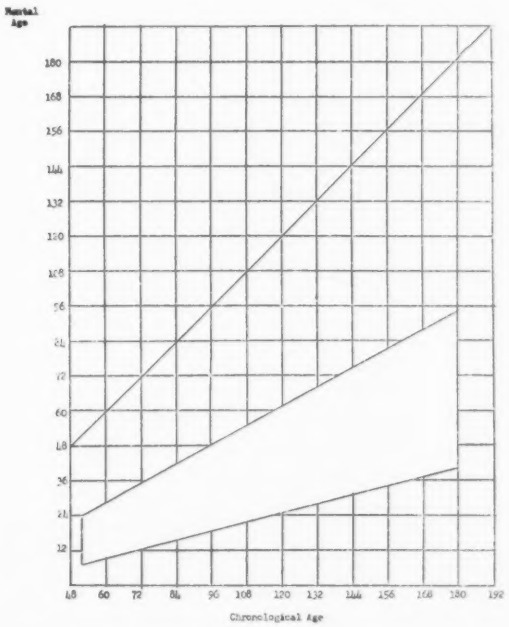

Fig. 1. Comparison of the variation and level of mental age between severely retarded children of different chronological age.

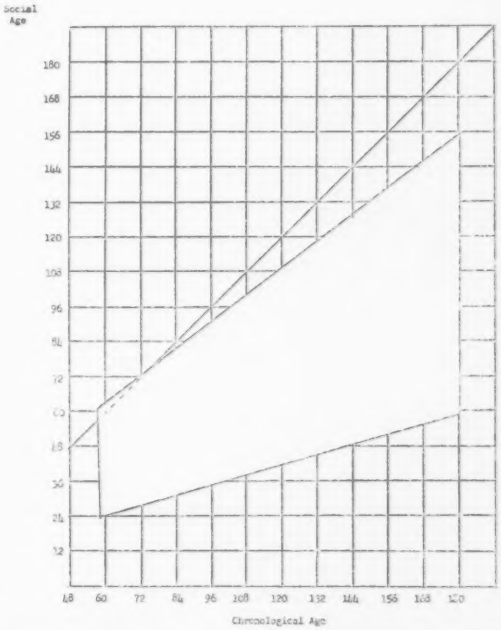

Fig. 2. Comparison of the variation and level of social age between severely retarded children of different chronological age.

but cautious consideration. The amount of mental growth is small for all of the children, and for a few it is very small. The mental ages of the children range from one-fourth to one-half their chronological ages. The brightest child has a mental age of seven and one-half years at fifteen years of age. If the child continues to grow mentally until he is twenty-two years old, he will have a mental age of eleven years. Certainly he will not be a completely adequate adult, but, all other things being equal, he need not be a completely dependent and socially useless person. A person with a 100 IQ and a mental age of eleven years is usually eleven years old and in the sixth grade. Anyone who has watched average sixth graders knows that they are capable of a great deal of simple, but to a large extent, independent living. They have enough speech to communicate, the ability to read the newspaper, the ability to play and work co-operatively, and the desire to be useful and productive.

We do not know at present how many severely retarded children would profit from a carefully planned educational program until they are 20 to 25 years old. A number of studies suggest the possibility of encouraging results. According to Freeman and Flory[1]:

> . . . children of mediocre ability continue to advance intellectually during the period of later adolescence, as rapidly if not more rapidly than do bright children, and they continue to advance to at least as late an age . . . children or youth of lesser promise may profit by continued education as much if not more than their precocious and brighter comrades. . . . The burden of proof is on the contention that the inclusion of children of lower ability would alter the picture. (p. 159)

Sarason[2] has this to say regarding the findings of a number of follow-up studies of retarded children:

> The misleading nature of diagnoses based on test scores is further revealed by the studies which have followed into adult life children who had been diag-

nosed as mentally defective when in grade school. . . . These studies showed that the academic achievement, economic self-sufficiency, and social adjustment of these groups were surprising in light of their original intellectual classification. (p. 107)

was then examined by a neurologist from the University Hospital. On the basis of data from the questionnaire and the results of his examination, the neurologist established the cause of each child's retarded condition. Eight main causes were identified. The causes, their description, and the percentage of cases under each cause are presented in Table I.

TABLE I.

CAUSES OF MENTAL RETARDATION AMONG 103 SEVERELY RETARDED CHILDREN

Cause	Description	Percentage of Cases
Structural defect (cerebral dysgenesis)	Brain failed to develop	25%
Familial	Intelligence normal for the family to which the child belongs	2%
Hereditary diseases (Tay-Sach's, von Recklinghausen's, Phenylpyruvia)	An inherited disease caused mental retardation	6%
Pre-natal damage (German measles, Rh incompatability, etc.)	Disease damaged the child before birth	10%
Birth damage (Prematurity, difficult delivery, anoxia, etc.)	Difficult delivery	20%
Post-natal damage (injury, encephalitis, meningitis)	Accident and injury during infancy and early childhood	8%
Clinical syndrome (mongolism, cretinism, and metabolic dysfunction)	Children whose appearance and health condition are invariably accompanied by mental retardation	18%
Cranial anomolies (hydrocephaly, macrocephaly, microcephaly, etc.)	The brain was damaged by a condition within the skull	7%
No known cause or conflicting diagnosis		4%

Social Growth of Mentally Retarded Children

The range of differences in social age at chronological ages five through fifteen for retarded children at the Coleman School is presented in Figure 2. As is true for mental age, the social ages of the older children are more advanced than those of the younger children. The differences among the older children are likewise greater than among the younger children. The social ages of the children do, however, exceed their mental ages.

Data on the social ages of the subjects of this study indicate that they are more capable of learning social skills than is commonly recognized. There are real limits, but nevertheless the children are capable of learning many of the simple niceties of life which enable people to live amicably together. It is high time that we apply to the retarded the mental hygiene principle that the social skills with which a person applies himself in daily living are as important as his knowledge and his academic and vocational skills.

As is the case for mental growth, the prospect of helping all retarded children acquire basic and minimal social skills is remote. The picture is one of wide differences in potential. The need is for opportunities to learn for those who can.

Causes of Mental Retardation

Early in the study a questionnaire was administered to the parents of the children. Each child

In all but two of the 103 cases mental retardation was associated with a preceding disease or accident. Pre-natal, birth, and post-natal damage accounted for 38 per cent of the cases. The findings indicate that a cure or prevention of mental retardation is a very remote possibility. As the national birth rate increases, the number of retarded children will increase proportionately. The problem of mental retardation will increase in the years immediately ahead.

Summary

It is strange that greater efforts have not been made to provide more severely retarded children with long-range educational programs. On the contrary, society has been remarkably effective in denying them opportunities. The emphasis has been on the provision of institutional beds and preparation for dependence. Enough data must be collected and used to show that many present policies and practices for severely retarded children are socially and economically unsound.

Data from the study to date suggest the following propositions regarding the care and education of severely retarded children.

1. It is more difficult than is commonly as-

sumed to predict the adult social status of severely retarded infants and children.

2. There is a great need for more experimental school programs for the severely retarded.

3. In order to make accurate estimates of the educability of some severely retarded children, there is a need for programs which can be sustained for a minimum of fifteen years with a stable enrollment which will permit longitudinal studies.

4. In any assay of the progress of retarded children it is better to use measures which show gain or loss with time (physical, mental and social ages) rather than measures which show status (intelligence and social quotients).

5. In teaching severely retarded children it is more rewarding to emphasize the maximum use of their assets than to seek methods to correct their deficiencies.

Findings from the first year of the study are neither startling nor conclusive. The tone of this report is positive but not intentionally unrealistic. It is hoped that the contents will serve to stimulate more awareness of the need for research on the care and education of severly retarded children. The study will continue during the 1957-58 school year. The promise of more significant and useful results appears to be good.

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PLANT HOSPITALS

Construction of two new medical units in Ford Motor Company's big Rouge manufacturing area, to replace the thirty-two-year-old hospital in the "B" building, culminates a series of studies started in 1952.

Ford's medical program dates back nearly fifty years to the early days of the Highland Park plant. At that time, the company had a staff of doctors and nurses and a hospital unit considered far better than average for its time.

Hospital facilities kept pace with the growth of the company and the first Rouge hospital was established in 1918 in a farm house that had been purchased with the land when the Rouge was being built. It was located near where the present Rouge office building stands. The staff was composed of four physicians and one extern.

This unit was outgrown within a few years and in January, 1926, the second floor of "B" building was taken over for a new hospital with modern equipment and larger staff.

From that time until it was closed a few weeks ago, the "B" building hospital handled a case load of nearly a quarter million annually—most of them minor injuries or illnesses.

Six years ago, at the suggestion of Henry Ford II, president, the company appointed an advisory board of four prominent physicians to re-examine the entire medical program, to make sure it was keeping abreast of the times.

Not long after the studies were completed, the company began instituting the recommended changes.

The final step in the program was construction of two new hospital units and abandonment of the old facilities in "B" building. Ground for the new buildings was broken in August, 1957, and construction was completed early in April, this year.

Hazards from Drugs Used in Obstetrics

By Norman F. Miller, M.D.
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THE ONE purpose of this discussion is to re-emphasize hazards sometimes resulting from drugs and drug-administration techniques commonly used in obstetric practice. Although these hazards are known, their universal acquaintance has not yet been achieved. If justification for this recapitulation of known facts is necessary, it may be found in the continuing reports, both published and unpublished, of complications and even deaths, resulting from the improper and sometimes too casual use of drugs in obstetrics.

In restricting this discussion to drug hazards, I am not unmindful of the usefulness of the drugs here to be discussed. Indeed, the one-sided presentation here contemplated must be prefaced by the acknowledgment that their benefits and good points far outweigh their drawbacks. Furthermore, hazards attributed to these drugs, are often more correctly assigned to faulty technique or improper dosage.

Most of us do not think of obstetrics as a field of extensive drug therapy. Yet, a perusal of indications suggests the contrary to be true. In obstetrics, as in all fields of medicine, the availability of new pharmacologic discoveries has increased drug usage. It has also permitted the attainment of more precise effects. As the usefulness and effectiveness of drugs have increased, the margin of safety has frequently decreased, thus emphasizing the need for ever greater vigilance. This emphasis upon *vigilance in the use of drugs* is precisely the function of this discussion.

Let us glance briefly at some of the accepted indications for drug use in obstetrics, thus: (1) control of nausea in early pregnancy; (2) correction of dietary deficiencies; (3) improvement of metabolic activity; (4) correction of anemia; (5) initiation of labor; (6) stimulation of indolent uterine contractions; (7) inhibition of over active uterine contractions; (8) production of analgesia; (9) induction of anesthesia; (10) reduction of hypertension; (11) inhibition or correction of hypotension; (12) control of shock; (13) combat delayed blood clotting (afibrinogenemia); (14) inhibition of blood clotting (phlebothrombosis and thrombophlebitis); (15) suppression of lactation; (16) stimulation of lactation; (17) control of infection; (18) reduction of nervous tension; (19) induction of sleep; (20) stimulation of infant; and (21) a variety of other purposes, too numerous to mention.

Before singling out drugs and techniques for special consideration, several generalizations seem worth mentioning. The human organism is by no means endowed with machine-like constancy. Consequently, unanticipated and extraordinary responses to drugs may be noted. Physician satisfaction with the effect obtained is by no means constant. This applies especially to drugs used for the relief of pain. Philosophy, then, regarding result desired, may greatly influence the amount of drug used. Modern medical practice calls less and less for direct administration of drugs by the physician, a fact which further dilutes our familiarity with their effects and side reactions. Because of these things, it is wise to carefully select those drugs with which we desire to work. Their continued use may then be based on a better understanding of their effects and defects. The dissatisfaction voiced against certain forms of medication is ofttimes the consequence of a too-diversified trial and error program. The use of drugs in obstetrics warrants particular vigilance because the maternal hemodynamics are altered from that of the normal nonpregnant state. Furthermore, since most drugs pass the placental barrier, every drug used in obstetrics must be weighed in the light of both its fetal and maternal responses.

Since hundreds of drugs are used in obstetrics it is obviously impossible to consider them all. Consequently, I have selected only a few for consideration at this time.

Chlorpromazine (Thorazine).—This popular drug has quite naturally found its way into ob-

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Presented at the Michigan Clinical Institute, Detroit, March, 1957.

stetric practice and has been used for the purpose of: (1) controlling nausea and vomiting in pregnancy, and (2) as a potentiator of sedative and analgesic drugs used during labor. The drug has a depressant action upon the central and autonomic nervous systems. Its ability to control or minimize some types of nausea and vomiting is now well known. However, the hazard of toxic hepatitis and jaundice from prolonged use warrants caution when used in obstetrics. It should be borne in mind that the antiemetic effect of chlorpromazine may mask or obscure the diagnosis of nausea and vomiting from other causes.

Chlorpromazine finds usefulness during labor as a means of potentiating and also reducing the amount of analgesic and sedative drugs required. In general 25 to 40 mgm. once or twice during labor as a supplement to other medication is sufficient. The use of chlorpromazine at this time may also aid in reducing the hazard of vomitus aspiration.

Since chlorpromazine has been known to produce hypotension following parenteral administration, its use in connection with saddle block, spinal or caudal anesthesia would appear to be contra-indicated. If regional block anesthesia *is* used following earlier administration of chlorpromazine, the likelihood of a blood pressure drop may be minimized by use of a vasopressor drug. Since epinephrin may show a reversal of action when used with chlorpromazine, nor-epinephrin (Levophed) is to be preferred.

While the use of chlorpromazine in obstetrics must await greater experience before being assigned to its final niche, presently it should be restricted to use during labor. Its use should be avoided in patients with liver damage, hypertension and/or cardiovascular renal disease.

Demerol.—Practically all sedative and analgesic drugs used for pain relief during labor pass the placental barrier to reach the fetus. This fact emphasizes the need to measure their usefulness and hazards by their effect upon both fetus and mother. Demerol has analgesic properties approaching that of morphine. While reasonable dosage (50 to 75 mgm.) repeated at two to four hour intervals during labor may cause no fetal respiratory depression, it should be remembered that later use of general anesthesia tends to accentuate any depressive effect upon the fetus. Demerol is well tolerated by most patients. Occasionally, however, shock-like reaction has been noted. This is characterized by pallor, sweating and hypotension. At least one maternal death has been reported following the intravenous injection of 100 mgm. The desirability of using a small initial dose in order to learn something of the patient's response is obvious. *N-Allylnormorphine Hydrochloride* (Nalline) is considered to be a specific antidote (5-10 mgm. intravenously), depending on the severity of the need. Obviously no patient heavily sedated, regardless of the drug used, should be left unattended.

Ether.—Much could be said regarding the use of inhalation anesthesia during labor. Much might also be said regarding the real need for an anesthesiologist or competent anesthetist in the delivery room. Since, by and large, their presence is only sporadically possible, the physician generally finds himself dependent upon other methods for the relief of pain during labor. When terminal inhalation anesthesia is needed, open drop ether, administered by the physician himself or by someone he designates, is the inhalant most frequently utilized. The occasional need for the physician to be both anaesthetist and obstetrician at one and the same time creates a real problem. Furthermore, since most patients in labor are poor general anesthetic risks, we have here an added hazard. The probability that the patient has partaken of food and fluids before entering the hospital definitely predisposes to aspiration of vomitus. The number of maternal deaths from this cause is by no means negligible.

Trilene (Trichlorethylene).—This nonexplosive liquid inhalant has found considerable favor for short use as an analgesic during the later part of labor. It is frequently used in conjunction with pudendal nerve block analgesia. The drug has a depressant action upon the higher brain centers and may cause depression of the infant. Trilene is commonly self-administered by the patient through an appropriate inhalor (Emotril or Duke), in weak concentrations (0.375 per cent-0.5 per cent concentration. It should be used as an analgesic and not as an anesthetic. Posterior pituitary extract and epinephrine must not be administered to patients receiving Trilene. Similarly, the inhalation of Trilene during labor contraindicates subsequent inhalation anesthesia by closed or semiclosed soda-lime absorption tech-

nique. Metabolic products produced by the reaction of these chemicals are toxic and have resulted in eighth nerve damage (deafness).

Regional Block Anesthesia (continuous caudal, saddle block or low spinal).—With these forms of pain relief, the technique of drug administration is about as important as the drug itself. Indeed, faulty technique is an important factor in the hazard attributed to drugs used for regional block anesthesia. Complications include: maternal hypotension, fetal anoxia, stopping of labor, post-anesthesia headache, increased use of forceps, irritated nerve-root phenomena, causalgia, foot drop, multiple myelitis, respiratory paralysis and death. The more serious complications have generally followed spinal anesthesia and occurred for one or more of the following reasons: (1) improper technique, (2) excessive dosage, (3) lack of close patient observation, (4) failure to observe contra-indications, and (5) use of wrong drug.

No one should undertake administration of the potent analgesic drugs used for regional block anesthesia without first becoming thoroughly familiar with the drug dosage and the technique advised for obstetric patients. These requirements are absolutely essential for safety. Failure to observe them has resulted in serious complications and death. That the pregnant woman at term requires *less* drug administration than in the non-pregnant state is now quite well established. This is explained on the basis of altered hemodynamics. In using low and safer dosage, analgesia may be achieved more slowly; therefore, the physician must exercise patience. For single dose spinal or saddle block anesthesia for vaginal delivery, no more than the following listed amounts should be given.

Procaine	30	to	50	mgm.
Metycaine	22	to	30	mgm.
Pontocaine	2	to	5	mgm.
Nupercaine	2.5	to	3.75	mgm.
Xylocaine	25	to	40	mgm.

For single injection spinal anesthesia for cesarean section Pontocaine up to 8 mgm. or Nupercaine up to 5 mgm. may be utilized. The shorter-acting Procaine, Metycaine, and Xylocaine are generally not suitable for this purpose.

Regional block anaesthesia techniques have much merit. They are especially rewarding in obstetrics, but they are precision techniques. They demand full comprehension of drug dosages for obstetric patients, exacting care in administration and constant patient supervision.

Posterior Pituitary Extracts.—Prior to present-day use in dilute form these powerful oxytocic drugs were responsible for serious fetal and maternal complications. The present technique for their use in dilute form represents a distinct improvement. However, this change from the old to the new has not eliminated all risk. Present usage calls for the dilution of 10 International units of posterior pituitary extract (Pitocin) in 500 to 1,000 ml. of 5 per cent glucose solution in distilled water. This is administered intravenously at 8 to 10 drops per minute at first, the rate of administration being increased gradually (25 to 40 drops per minute), depending on uterine response. When justifiably indicated and carefully scrutinized, this technique has proven satisfactory for the induction of labor and the treatment of inertia in selected patients. However, the tetanic activity of the hyperresponsive uterus serves to remind us that even in minute amounts this drug may precipitate untoward action. Constant observation of the patient during the period of administration is essential. Abrupt and abnormal rise in blood pressure has also been noted. In susceptible patients such rise may be especially unfortuitous.

Since the apparatus used for intravenous administration of posterior pituitary extract is not standardized, it is important to use an arrangement which permits prompt stoppage of the drug if necessary. This may be accomplished by a double stopcock near the point of vena-puncture, thus permitting switch to plain glucose solution, or the single tube technique may be used, in which case an available bottle of dextrose solution may be hooked up to the needle in place of the dilute pituitary solution. With care in administration and close observation, rupture of the uterus should no longer occur.

Ergot Alkaloids.—The ergot alkaloid, ergonovine maleate (Ergotrate) and the semi-synthetic preparation, Methyl-Ergonovine tartrate (Methergine) have achieved such general acceptance in obstetrics that today physicians look upon their use as essential to the proper conduct of labor. While their potent ecbolic effect far outweighs their disadvantages, we need to be reminded that

these drugs—as commonly used in obstetrics—are neither essential nor without hazard. The ergot alkaloids should only be used after delivery because of their uncontrolled and prolonged oxytocic effect. Side effects sometimes noted include prompt and significant rise in blood pressure within seconds following intravenous injection. This may be accompanied by nausea, vomiting, tinnitis and flushed skin. The need to avoid hypertension in patients with toxemia, suspected aneurysm, and other cardiovascular diseases is obvious. Similarly, induced vomiting could be a hazard for patients who are to receive inhalation anesthesia. These untoward effects are uncommon and inconsistent.

Summary

It has been the purpose of this brief discussion to re-state certain drug hazards in obstetrics. There are many others. In order to reduce these hazards it is well to acquire a rule-of-thumb philosophy regarding the use of any drug in obstetrics. To this end the following suggestions are appended.

1. The increased variety, potency and specificity of drugs permit us to achieve improved therapeutic response, but generally at the expense of requiring greater precision and vigilance in the techniques of their administration.

2. From a practical standpoint, it is better to work with a few selected drugs in order to achieve familiarity and safety in their use.

3. Before using any drug, learn the elements of its pharmacologic action, dose, indications, technique of administration, and possible hazards and antidote.

4. Since most drugs pass the placental barrier, all medication administered to pregnant women should be evaluated on the basis of both fetal and maternal effect.

5. Remember, the obstetric patient generally requires less drug (especially drugs used in regional block analgesia) than the accepted standard dose used for the non-pregnant state.

6. While most drugs are administered by others on a physician's order, the responsibility, regardless of end result, remains with the physician.

7. Never permit a pregnant patient who is receiving a potent drug, to be left unattended.

BLUE SHIELD BENEFITS

"One of the few constructive, forward steps taken by the medical profession in the last twenty years has been the adoption of Blue Shield. It may represent one of our few hopes for survival as a self-determining profession. In theory, its original aim was to convert a system of postponed payment for medical service into a streamlined system of prepayment for protective care. This was intended to confer a benefit on the public by allowing low-income groups to share the full advantage of private medicine—and at the same time, the profession would gain the benefit of converting a large amount of charity service into paying practice. Both these theoretical benefits have been so realistically vindicated in the experience of the last two decades that they now stand above debate. But today a third and still more important benefit from Blue Shield is becoming more and more apparent, for this service has given us an intelligently co-ordinated and profesisonally controlled corporate body through which we can bargain with the public and they with us."—CHARLES H. BRADFORT, M.D., *The New England Journal of Medicine*, April 3, 1958.

* * *

"Blue Shield is a product of the Massachusetts Medical Society and was originated as a constructive step toward making medical care available to all, and to act as a bulwark against the encroaching tide of governmental subsidization. Society and Service must work together in amity and in close co-operation if the system of free enterprise is to survive."—DAVID ROSE, M.D., *New England Journal of Medicine*, May 1, 1958.

Editorial

IMMUNIZATION

In 1887, the *Journal of Physiology* carried an article entitled "Experiments on the Preventive Inoculation of Rattlesnake Venom" by Henry Sewall, Ph.D., Professor of Physiology in the University of Michigan. In it he speculates:

> "If immunity from the fatal effects of snake-bite can be secured in an animal by means of repeated inoculation with doses of the poison too small to produce ill effects, we may suspect that the same sort of resistance against germ-disease might follow the inoculation of the appropriate ptomaine, provided that it is through the products of their metabolism that bacteria produce their fatal effects."

In beautifully controlled experiments, Sewall demonstrated that guinea pigs could be made immune to large amounts of venom as a result of the repeated small doses which they could tolerate. The immunity which developed persisted at least for five months. These demonstrations became the basis of antitoxic immunity. Dr. Victor Vaughan relates the visit of distinguished French scientists to Ann Arbor some years later to see where the work had been done which pointed out the way to the discovery of diphtheria antitoxin, and also the basis for active immunization with toxins.

It is interesting that these studies were conducted by a physiologist for the mechanisms of resistance to infection are so clearly physiological in character although study of the processes until recently has been carefully avoided by physiologists. The principle of active immunization is to induce resistance comparable or even superior to that which can result from the full blown disease without experiencing the ill effects of disease. Much of this is accomplished in nature by subclinical infection but it is an unpredictable method. Vaccination against smallpox, rabies, or yellow fever represents the establishment of infection with modified or attenuated viruses which induce immune responses capable of protecting against the fully virulent agents. Immunization against diphtheria and tetanus is induced, as Sewall foresaw, with products of bacterial metabolism. Still other vaccines contain killed whole viral or bacterial bodies which retain the biochemical components or antigens essential to stimulate the specific, protective antibodies—influenza, poliomyelitis, pertussis. One can look forward to the compounding of vaccines which will contain only the purified antigens extracted from infectious agents without the mass of non-essential matter present in the bacterial body. As the causes of many more diseases are recognized and the make-up and modes of action of these agents are better understood, advanced technical methods will result in additional preventive vaccines. Their applicability will raise further the necessity for multivalent preparations effective against a number of different diseases.

Preservation of the norm and prevention of disorder is a fundamental concept of immunology and immunization. It has been a continued objective in Michigan medicine since Sewall and Vaughan. The first full chair of Hygiene was established at the University of Michigan in 1887, and in January, 1889, the Hygienic Laboratory—first of its kind in the nation—opened its doors. In 1903, a Pasteur Institute for the study and control of rabies was established. The laboratories of the State Department of Health became a producer of biological products of unsurpassed excellence. In their laboratories, Doctor Kendrick and Doctor Eldering produced the material and conducted the studies which established the value of pertussis vaccine. The investigation and development of influenza vaccine has been a continuing activity of the Department of Epidemiology at the University of Michigan. It also played an important role in evaluation of the Salk vaccine for poliomyelitis. Doctor Nungester continues with efforts to provide improved materials generally applicable to the prevention of tuberculosis. Control of disease by immunization is, then, a Michigan heritage.

Preventive medicine has frequently been called the medicine of the future. The current opportunities to prevent disorders indicate that the future is close at hand.

THOMAS FRANCIS, JR., M.D.

Dr. Francis is Henry Sewall University Professor of Epidemiology, Chairman of the Department of Epidemiology, School of Public Health, and Professor of Epidemiology, Department of Pediatrics and Communicable Diseases, University of Michigan Medical School.

This Is It!

We took a Long Look at the Problem.

Now let's take a Good Look at the Answer.

Because a change in Michigan Medical Service was long overdue, our Society wanted to find out what the public and the profession wanted in prepaid medical care before it took action. In effect, we said: "Let's plan for the future from *knowledge;* not jump to meet the exigencies of the moment."

Our scientific and comprehensive Opinion Study gave us the wishes of the public and the instructions of our membership, and our policy makers acted to give us an answer. The answer has two parts—one is the statement of principles, the other the MMS contract to implement the directives inherent in those principles.

This MMS contract, having followed the House of Delegates' Statement of Principles to the letter and having been duly approved after the most exhaustive study by proper authorities, is now in the hands of subscribers. But more importantly, it is in your hands and mine as practicing doctors of medicine. It is worthless unless we need it, want it, use it, support it, guard it, buy it and sell it.

Let me go on record as saying: "This is it. It is the finest answer which can be fashioned at this time and in these circumstances by human ingenuity and skill to meet this medical-economic problem. I'm for it unequivocally and without reservation."

Join me. Not with tongue-in-cheek, not with mental reservations, not with a "sacrifice complex," but enthusiastically, willingly, and a let's-make-it-the-biggest-success-yet spirit.

Don't mistake me. I don't believe all our problems are solved. I don't believe they will be, even if this program is 100 per cent perfect. (Time will develop new problems, to be sure.) But if we do give this program our confidence, I know we shall make progress.

Geo. K. Slagle.

President, Michigan State Medical Society

President's

Message

APPRECIATION

We wish to thank Dr. Thomas Francis, Jr., and his staff for their invaluable aid in preparing and selecting the material for this special issue on immunization.

SOME COGITATIONS

The Michigan State Medical Society is offering a completely new concept of medical services contract for the people of the State of Michigan, involving numerous untried principles and a new approach to service to our over 3,750,000 subscribers. The details of the plan are being determined and implemented by a group of Michigan State Medical Society members devoting many full-day sessions trying to match action and accomplishment with the expressed decisions growing out of the Opinion Survey made in 1957. This committee and the staff of Michigan Medical Service have available and are using the finest actuarial and insurance counsel available. After expressing the final details of the contract according to instructions, the relative value scales have been readjusted to meet Michigan conditions, the details and items are sufficiently known that comparison can be made showing an increase in benefits for services in the $7,500 certificate of about 32 per cent over the rates of the old $5,000 certificate. For general distribution, a 250-item listing of the new relative value scale is now in process of publication. When the final details of listing were accepted the Council adopted the fundamental program and authorized application to the Insurance Commissioner for final approval which then granted will include the new ratings.

Some members, and some closely organized groups are disregarding the fact that they had been asked repeatedly to submit rates and fee schedules to the working committees which were appointed to establish fair, adequate schedules. The last revision was made in 1949, but modifications of some items have been made regularly ever since. Persons are publishing through letters and other mediums, disgruntled and disturbingly inaccurate charges tending to produce disunity and discontent with the new program. Tape recordings of the meetings referred to disprove and fail to show some quotations which are being distributed. The members being attacked and criticized have devoted untold nerve-wracking days trying to assure the most complete and accurate attainment of the expressed wishes and desires of the membership and of the people demonstrated by this 1957 survey mentioned before as the basic guide.

Commendations-condemnations

These are two very similar words with almost exactly the same letters, but what a difference in meaning. The Michigan State Medical Society has several committees which over long periods have been meeting frequently, spending days and nights doing the necessary work of the Society, expressing and carrying out its ambition and expressed desires. That especially includes this one committee which is now under severe criticism by persons who (we hope) misunderstand. These devoted, hard-working members, instead of condemnation, actually merit the highest commendation possible to give.

The Michigan State Medical Society and the medical profession in general are now recognizing another trend toward governmental, bureaucratic or pressure group efforts to dominate and administer medical services. To retain to the medical profession the direction of the pre-paid insurance features and the modernization and expansion of the benefits being demanded, this entirely new program is being offered. Nineteen years ago the very strongly intrenched bureaucrats and social leaders almost accomplished the federalization of the medical profession, but Blue Shield at that time saved private practice.

The Michigan State Medical Society was then entering into an entirely new and untried field, the application of insurance principles in providing medical care. Before being allowed to proceed, the State Insurance Commissioner demanded evidence that the medical profession would actually give the benefits being promised to the people who might subscribe. Eighty-two per cent of our doctors of medicine signed "participation" slips agreeing to accept as full payment for the under-income-limit persons, the fees which the Plan had established and hoped to pay. Participation was a purely voluntary action but a necessary one to start the pre-paid medical service plan. The Michigan State Medical Society was lucky and fortunate that so many of its members had faith. The socializing, federalizing process then so far advanced was effectively postponed and almost completely forgotten by too many members.

The new and modernized program now being offered must also have a sufficient number of

participating members to guarantee its success. There is not now the same risk to assume. Blue Shield probably never will have to prorate payments to the members as so many plans did in the early, formative years and as Michigan did for a period of a few months. Medical leaders not only in Michigan, but throughout the land, believe the profession is again facing grave forebodings which must be met and solved. They are again looking to Michigan to lead the way.

Participation

"Participation" is now being solicited—no one is compelled to sign. It is absolutely voluntary. No person, no group has "fixed the amount of pay the doctor must accept." A suggested adequate schedule of benefits has been listed for the services which the Society, through its House of Delegates, is promising. Remember, there are numerous benefits which the participating doctor —as well as the patient—will receive. Under the old ordinary insurance plan, indemnity was paid to the patient and the doctor had his collection expenses. One of the first principles and reasons stimulating the early establishment of Blue Shield and the pre-payment plans in general, was to guarantee money would be available to pay for the services which the patients need. The payments would be made directly to the doctors.

Each member must make his own determination, his own choice. The Society believes and hopes that more than the original 82 per cent of its membership will have faith in the professional administration and again stave off the the disrupting forces without and within which are so insistent and threatening.

Practically all the conditions and desires expressed by the survey and the medical questionnaire have been accomplished in the completely modernized version of the Blue Shield Plan. There always have been and probably always will be minor compromises which different interests must make but the final accomplishments in our new principles and concept of service are unusually complete and conforming. Non-participating members of our Society and the large groups of non-members actually and basically become participators because they express by usage of the plan their confidence of collecting their account without effort.

A man who is not willing to take his chances of collecting fees from his patients when he knows insurance has been paid is not consistent. Prepaid "medical benefits" insurance guarantees full payment of the amount established by the Michigan State Medical Society.

The new pre-payment medical program is a program of Michigan State Medical Society; participation is with the Michigan State Medical Society. Michigan Medical Service is the administrating group carrying out the ideals of the Michigan State Medical Society. Remember?

In the middle 1930's, there were health and accident insurance companies with policies which paid weekly benefits to the disabled or ailing subscribers to an amount usually of $25.00 This was paid direct to the insured and in those years of scarce money, few jobs, insecurity in general, the problem of collecting for medical services rendered was a real one and was a considerable expense to the doctor. A very concerted effort was made by the Michigan State Medical Society to induce insurance companies to pay the doctor direct or by a co-signed check to the doctor and to the beneficiary. After years of efforts such agreements were made by a majority of the insurance companies doing business in Michigan. Similar actions were taken in other states. That was a great accomplishment and widely publicized to the profession. It was then necessary, however, for the patient or the insurance beneficiary, to sign a waiver to the insurance company. That arrangement helped in the development of our voluntary pre-payment plans. Insurance companies were asked to set up such a program but claimed it was not actuarily sound.

Would you like to return to the 1930's with their insecurity—their collection costs and inconvenience—no one budgeting medical costs?

DIVIDE AND CONQUER

There is increased apprehension among the medical leaders and statesmen throughout the nation regarding the constant trend toward government medicine, of the invasion of pressure groups, labor and others, who wish to dominate the dispensing of health services.

Each year sees large groups of people removed from the clientele of the private practice of medicine. Some have been taken over by government. Probably the most threatening just now are the

labor-controlled groups which are using closed panels of salaried medical men.

How is this being accomplished? By the old method of *divide and conquer*. The original Wagner-Murray-Dingell bill, which caused so much trouble on the state and national scene, several years ago is being enacted by piecemeal methods, thereby making great inroads in private practice. It is now apparent that more and different controls are being considered by much more closely entrenched leaders who will use every strategy to get one advantage after another—with the whole pie their ultimate goal.

Blue Shield and Blue Cross are still the saving buffer which retained the profession in private practice.

The whole medical profession is in the balance. It must act concertedly and unanimously or one disgruntled or even wavering group after another will weaken the whole defense. Now is no time for disunity. In the late 1930's the profession almost completely stood its ground and won. It might do so now.

We are one profession—divided into specialties and groups, but with one fundamental goal. As never before the profession now needs "unity."

LOOKING FORWARD

The Editor wishes to offer a purely personal and possibly selfish expression of his feelings, reactions and visions of the impending future in medicine. For years, he has had an urge to write a book, in fact twice has started one, but was interrupted and dissuaded by other interests and never finished. Besides helping record the present has been fascinating and rewarding. He has been attentively attending medical meetings, and many, many times—almost always—returns home with the feeling of having learned something new, and that, frequently, from the chance conversation with a friend old or new. He has recently spent four full days and five nights in Detroit at the Twelfth Michigan Clinical Institute. Again he has unbounded enthusiasm. He has sat three or four hours at a stretch listening to research workers and practitioners picture the past and future of medicine.

The theme "Yesterday's Hopeless—Now Curable" was a stroke of genius. The terrific storm in the East necessarily concentrated a group of speakers into the final afternoon (Friday, March 21) and gave the small group of members who stayed to the end, a treat never to be forgotten.

The miracles being accomplished by skilled masters in so many conditions heretofore almost always considered hopeless was truly inspiring. We came away with an intense awareness of astounding accomplishment almost upon us—really happening before our eyes. We have seen the antibiotic drugs, the miracle preparations and their tremendous gifts of life in the last few years. We have seen surgery enter the heart, the great blood vessel, the chest, the neurological system. Each with such a realistic effect gives more and more abiding hope to the recipient. We have marveled and applauded and have been especially touched by the amazing contribution of our own friends and neighbors which have added to the overall picture. We have seen two pioneer television exhibitions that were not only the first but have illustrated to millions of viewers what scientific medicine is accomplishing.

The promises made to the small group Friday afternoon should have reached every member. They gave us a feeling that many new answers of research are just about culminating. New hope is offered in toxemia of pregnancy—its diagnosis and treatment, in diseases of the nervous system, in acute infectious diseases, in allergies, in dermatology, and a hint that cancer is being attacked from a different angle—maybe not a new thought—but certainly encouraging.

Are the allergies and cancer states of mind or diasthenoses? Listeners were given the intimation that newer modified concepts are showing results in both fields.

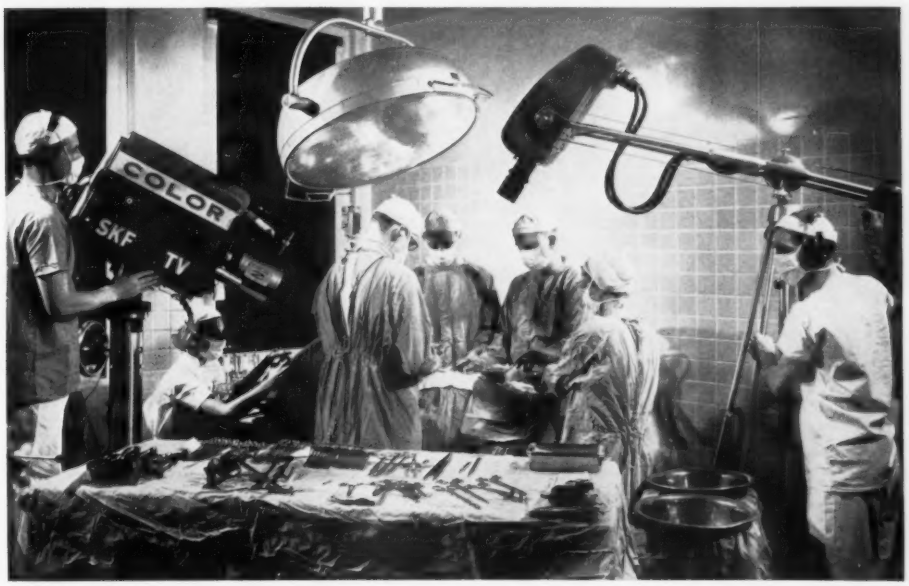
It was inspiring, and the Editor hopes the printed reports will carry the hopeful messages (sometimes given aside) to the hundreds who did not stay.

We wish to pay tribute to Paul deKruif, Sc.D., who was instrumental in securing several of the outstanding speakers, especially on the last day's program. He had been assigned chairmanship of the final quiz conference, stayed in the forefront of the dwindling audience, encouraged everyone. The final gesture was typical of his forethought. The session had run more than an hour over time, due to late start and snow. He called the meeting to order immediately, made a few very complimentary remarks about the wonderful papers, and dismissed the group.

Paul, we admire and thank you.

MCI Live Surgery Viewed by Two Million

As a prelude to the 1957 Michigan Clinical Institute on March 19, nearly two million television viewers watched a Detroit surgeon replace a diseased artery with a dacron substitute.



The live hour-long show was telecast in compatible color by WWJ-TV and transmitted to a statewide network of TV stations including those in Cadillac, Grand Rapids, Lansing and Traverse City.

The actual operation was performed in Henry Ford Hospital where the scene was picked up by the mobile color TV cameras of Smith, Kline & French Laboratories, Philadelphia. By microwave relay, the picture was sent to the WWJ-TV studios for transmission to the thousands of home sets awaiting the second live operation ever to be publicly telecast in Michigan.

Few of the MCI registrants, totaling 2,885, missed the Tuesday night broadcast, though not all were able to view the program on color television receivers. MCI and Michigan State Medical Society officials were gratified at the overwhelming public acclaim which followed the broadcast.

While the surgical team worked under the direction of D. Emerick Szilagyi, M.D., and Roger F. Smith, M.D., a panel of doctors of medicine was ready at intervals in an adjoining studio to explain in lay terms what the public had just seen on the screen. The panel was composed of Henry T. Bahnson, M.D., Associate Professor of Surgery, Johns Hopkins Hospital, Baltimore; Marion DeWeese, M.D., Associate Professor of Surgery, University of Michigan, Ann Arbor; Prescott Jordon, M.D., Associate Professor of Surgery, Wayne State University, Detroit; and Eugene A. Osius, M.D., Chief of Surgery at Harper Hospital, Detroit.

MSMS Honors Thirteen

Mid-way during the Michigan Clinical Institute proceedings, the Michigan medical profession paused to pay tribute to six doctors of medicine and seven prominent citizens who had made significant contributions in the broad field of health.

Chairman of the testimonial luncheon was Kenneth H. Johnson, M.D., Lansing, who introduced the guest speaker, The Honorable James E. Haggerty, president, State Bar of Michigan.

Presentations of the scrolls were made by George W. Slagle, M.D., and L. Fernald Foster, M.D.

Serving as the Committee on Arrangements and also doing double duty as host to the honorees were: Kenneth H. Johnson, M.D., Lansing; Lester P. Dodd, LL.B., Detroit; B. M. Harris, M.D., Ypsilanti; Robert G. Jaedecke, M.D., Ishpeming; William S. Jones, M.D., Menominee; Ivan A. LaCore, M.D., Pontiac; Claude A. Ludwig, M.D., Port Huron; Robert L. Novy, M.D., Detroit; C. Allen Payne, M.D., Grand Rapids; Horace Wray Porter, M.D., Jackson; A. E. Schiller, M.D., Detroit; John M. Sheldon, M.D., Ann Arbor; George W. Slagle, M.D., Battle Creek; D. Bruce Wiley, M.D., Utica, and H. B. Zemmer, M.D., Lapeer.

William J. Burns, MSMS executive director, was recognized as an honorary member of MSMS. The *Battle Creek Enquirer and News* was saluted for sponsoring a series of public health forums. For co-operation in telecasting the 1957 public colorcast of the live heart surgery, WWJ-TV was presented with a scroll of appreciation. The four legislators were honored for their longtime support of health-welfare legislation in Michigan.

With obvious enjoyment, Frederick A. Coller, M.D., accepts his scroll from George W. Slagle, M.D.

K. H. Johnson, M.D., luncheon chairman, greets *(left to right)* Representative Cramton, Senator Christman, Senator Nichols, and Representative Harry Phillips.

R. B. Miller is pinned by MSMS president as luncheon speaker James E. Haggerty, State Bar president and Honoree Joseph G. Molner, M.D., look on.

Honorees William J. Burns, MSMS executive director, and Grover C. Penberthy, M.D., check the luncheon program.

at Testimonial Luncheon

HONOREES

O. A. Brines, M.D., *Detroit, President International Society of Clinical Pathology*

A. C. Furstenberg, M.D., *Ann Arbor, Dean, University of Michigan Medical School*

Edgar A. Kahn, M.D., *Ann Arbor, President, Society of Neurological Surgeons*

Joseph G. Molner, M.D., *Detroit, Author of nationally-syndicated medical column*

Grover C. Penberthy, M.D., *Detroit, Chairman, Selective Service in Michigan*

Paul Van Riper, M.D., *Champion, Michigan's Foremost Family Physician for 1957*

Mrs. Samuel Dibble beams as her father, Paul Van Riper, M.D. (Michigan's Foremost Family Physician—1957), is congratulated by C. E. Umphrey, M.D., MCI general chairman.

AWARDEES

William J. Burns, LL.B., *Lansing, MSMS Executive Director*

Battle Creek Enquirer and News, R. B. Miller, *Publisher*

Senator Lewis G. Christman, *Ann Arbor*

Representative Louis C. Cramton, *Lapeer*

Senator Haskell L. Nichols, *Jackson*

Representative Harry J. Phillips, *Port Huron*

WWJ-TV, *Detroit*

Don De Groot, *Assistant General Manager*

MSMS Awards Committee Chairman L. F. Foster, M.D., admires scroll presented to each honoree, *(left to right)* E. A. Kahn, M.D., A. C. Furstenberg, M.D., and O. A. Brines, M.D.

Detroit Service Clubs Hear

Kenneth Mathews, M.D., Ann Arbor, chats with club members following his talk before Detroit's Central Kiwanis Club.

G. Brinkman, M.D. *(center)* chats with president of Downtown Lions Club.

James S. Feurig, M.D. *(center)*, East Lansing, with officers of Detroit Riverside Kiwanis Club.

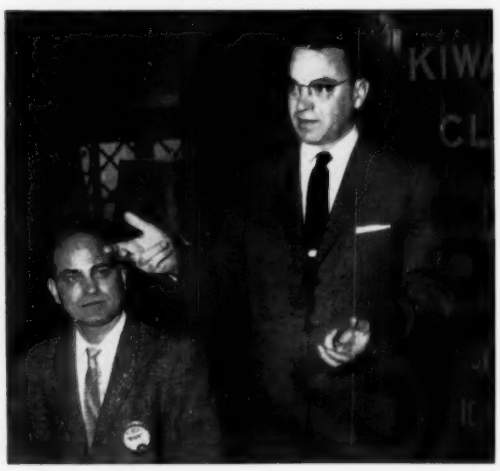
Nearly 3,000 Rotarians, Kiwanians and other Detroit area service club members heard talks by doctors of medicine during the week of the 12th Michigan Clinical Institute in mid-March.

Speaking engagements were arranged by the MSMS Public Relations office in Detroit.

Topics ranged from Aorta to Mental Health, but all talks carried some report of the purpose of the annual MCI refresher course. Club interest in the programs ran high because of the stimulus of the public telecast, in color, of an aortic transplant performed before an audience of more than two million Michigan televiewers. The operation was performed in Henry Ford Hospital and beamed to WWJ-TV for transmission to a statewide TV network. Technical production of the public show and daily closed circuit broadcasts during the MCI program were handled by a special TV crew of Smith, Kline and French Laboratories.

In all, twenty-nine service clubs were reached by medical spokesmen. Typical of the comments received from club program chairmen is this from John C. McCurry, program chairman of Detroit Rotary, who said, ". . . we had a standing-room-only crowd, and it is seldom that I have ever seen a speaker hold the interest of his audience as did our doctor guest last Wednesday. Thanks to all those responsible for making this address possible."

George W. Slagle, M.D., MSMS president, addressing Grosse Pointe Kiwanis Club.



Medicine's Story During MCI

KIWANIS CLUB OF DENBY DETROIT (Perrini's Restaurant): D. Emerick Szilagyi, M.D.—"New Arteries for Old"

HAMTRAMCK ROTARY CLUB (Polish-American Century Club): Clarence Owen, M.D.—"Responsibility of Doctor to Hospital, and Vice Versa"

FORT ALLEN KIWANIS CLUB (Wabeek Tea Room, Wyandotte): E. A. Osius, M.D.—"Vascular Surgery"

PONTIAC HI TWELVE CLUB (Masonic Temple, Pontiac): Brooker L. Masters, M.D.—"Blue Cross-Blue Shield"

U & I CLUB (Detroit Leland Hotel): A. S. Church, M.D.—"A Psychiatrist Looks at Our Culture"

LOLA VALLEY KIWANIS CLUB (E & K Dining Hall): C. J. Hipps, M.D.—"Plastic Surgery"

CENTRAL KIWANIS CLUB (Abington Hotel): Kenneth Mathews, M.D.—"Allergies"

NORTH DETROIT KIWANIS CLUB (Lutheran Institute for the Deaf): Glenn E. Millard, M.D.—"Heart Disease and High Blood Pressure"

HARPER WOODS KIWANIS CLUB (Notre Dame High School): Benjamin Jeffries, M.D.—"Mental and Emotional Problems"

WARRENDALE KIWANIS CLUB (Evergreen Lutheran Church): Carl J. Sprunk, M.D.—"Medicine in Civilian Defense"

NORTHEAST KIWANIS CLUB (Northeast YMCA): Paul R. Dumke, M.D.—"Anesthesia—Yesterday and Today"

DOWNTOWN LIONS CLUB (Statler Hotel): G. Brinkman, M.D.—"Lung Cancer and Cigarettes"

PONTIAC KIWANIS CLUB (Waldron Hotel, Pontiac): Prescott Jordon, M.D.—"Hypertension" and "The Live Telecast"

GROSSE POINTE KIWANIS CLUB (Grosse Pointe War Memorial): G. W. Slagle, M.D.—"The National Health Picture"

DEARBORN OUTER DRIVE KIWANIS (New Apostolic Church): J. R. Rodger, M.D.—"Traffic Safety and You, the Driver"

THE TRIMZ CLUB (Cannon Memorial Recreation): R. S. Knox, M.D.—"Emotional Problems of Overeating"

DETROIT ROTARY CLUB (Statler Hotel): D. Emerick Szilagyi, M.D.—"New Arteries for Old"

ART CENTRE KIWANIS CLUB (Belcrest Hotel): G. B. Saltonstall, M.D.—"Surgery Techniques"

VORTEX CLUB OF DETROIT (Harmonie Club): Roger Smith, M.D.—"Explanation of TV Show"

OAK PARK KIWANIS CLUB (Micheles Restaurant): A. H. Hirschfeld, M.D.

PONTIAC NORTH KIWANIS CLUB (Moose Lodge, Pontiac): Wm. M. LeFevre, M.D.—"The Businessman's Heart"

DELWOOD KIWANIS CLUB (Major's Cafe): Harry A. Towsley, M.D.—"The Doctor's Postgraduate Medical Education"

LIVONIA KIWANIS CLUB (Livonia Inn): Eugene Brooks, M.D.—"Psychiatric Perspectives on Criminality"

EXCALIBUR CLUB (Sheraton-Cadillac Hotel): Marion DeWeese, M.D.—"Explanation of TV show"

WEST PONTIAC KIWANIS (Scrib's Restaurant): E. J. Tallant, M.D.

DETROIT RIVERSIDE KIWANIS CLUB (Whittier Hotel): James S. Feurig, M.D.—"Medicine and Sports"

ROSEVILLE KIWANIS CLUB (Trinity Methodist Church): R. I. McClaughry, M.D.—"Medicine in the Community"

CENTERLINE ROTARY CLUB (Centerline Recreation): Aloysius Church, M.D.—"A Psychiatrist Looks at Our Culture"

Marion DeWeese, M.D., Ann Arbor, speaking before members of Detroit's Excalibur Club.

G. B. Saltonstall, M.D. *(center)*, MSMS president-elect, at the Art Centre Kiwanis Club, Detroit.

D. E. Szilagyi, M.D. *(right)* receiving thanks of Detroit Rotary Club program chairman, John C. McCurry.

Michigan's Department of Health

Albert E. Heustis, M.D., Commissioner

STAPHYLOCOCCAL INFECTIONS AND PUBLIC HEALTH

Staphylococcal infections, particularly in newborn infants, have been recognized as a public health problem for a good many years. The fact that these infections have become of increasing concern in the past few years is primarily a result of the development of antibiotic-resistant staphylococci which has, in turn, led to the creation of carriers of the organisms, frequently among hospital personnel.

From a public health standpoint, the Michigan Department of Health is most concerned about the hospital nursery problem. An outbreak of epidemic staphylococcus in the nursery, in addition to threatening infants' lives, can provide an avenue of infection to the family. These infections often persist for long periods of time and can spread out from the family to involve an entire community. Thus the possibility of widescale infection from infants exposed in the hospital nursery during an outbreak is very great.

Over the past two years, the Michigan Department of Health has investigated nineteen outbreaks of staphylococcus disease in hospital nurseries. In fifteen of these hospitals, located in eleven different counties, a single epidemic strain of the organism was identified: staphylococcus phage type 42B/52/80/81. In the other four hospitals, no single strain of staphylococcus was demonstrated to be the cause. However, in these four hospitals, conditions were such that gross contamination was possible. Correction of these conditions ended the outbreaks.

In all the outbreaks investigated, there was one relatively common factor: overcrowding of the nursery. In most of these nurseries the space between bassinets was considerably less than the 2 feet recommended. As a result of this overcrowding there was increased activity in the nursery by a greater number of staff persons thus increasing the possibility of initial infection and the likelihood of infant to infant transfer.

In the majority of the epidemic outbreaks investigated in which a single strain of staphylococcus was identified, one or more carriers of the specific epidemic type was found to be in daily contact with the infants. Techniques to prevent infant to infant spread combined with removal of the carrier or carriers prevented the occurrence of further outbreaks.

The epidemic type of staphylococcus disease manifests itself in several ways, but primarily through pustules on the skin although it may also result in sepsis, pneumonia, or abscess of the infant breast. The second major expression of the disease is the occurrence of breast abscesses in mothers. Third is the occurrence of infections of wounds of surgical patients. Fourth is infection of the skin and/or lungs of bedridden chronic patients.

The known occurrence of epidemic outbreaks of staphylococcus disease in Michigan in nurseries has been in hospitals in which there were over 30,000 births annually. However, the problem of staphylococcus infection is not limited to the nurseries. For example, the disease may occur in surgical patients and may also result in food poisoning. Surgical patients may develop membraneous enterocolitis as a result of antibiotic-resistant staphylococcus acquired in the hospital. These organisms are able to grow in the bowel because the normal bowel bacteria have been destroyed by antibiotics, chiefly the tetracyclines, so that surgery might be accomplished more successfully. Food poisoning may result from the toxins which certain types of staphylococcus elaborate. These may get into the food from an infected finger or from the nose and throat of the cook or other food service personnel who are carriers. In certain foods such as custards, or hams, these organisms tend to grow. Although the organisms may be destroyed by the heat of cooking, the toxins they produce are not affected.

From a control point of view, the Department feels that the mainstays of prevention are:

1. Rigid standards of cleanliness.
2. Aseptic techniques.
3. Alertness to the possibility of the problem developing in the nursery and prompt isolation of infants suspected of having an infection.
4. In the hospital a committee on infection with delegation of one member of the medical staff as the person specifically responsible for carrying out measures to control the problem.
5. Determination of sensitivity and use of that antibiotic which is effective in controlling the organism where treatment is necessary.

Unquestionably, staphylococcus infections have become a major problem, usually first recognized in the community's hospital. Assistance from the Michigan Department of Health can be obtained by any Michigan hospital which has a problem with staphylococcus infection.

RULES AND REGULATIONS FOR NURSING HOMES AND HOMES FOR THE AGED

(Excerpts Applying to Medical Supervision)

Each patient or resident admitted to a home shall be examined by a physician before or promptly after admission in order to safeguard against contagion and to insure needed medical care.

This examination shall include a chest x-ray.

Each patient in a nursing home shall be under the continuing supervision of a licensed physician.

(Continued on Page 754)

NURSING HOME RULES

(Continued from Page 752)

The operator of a home shall be responsible for arranging for the prompt provision of this and any other needed medical care.

Nursing homes shall require an admitting diagnosis and treatment plan to be recorded promptly for each patient admitted.

All treatment shall be under the specific or standing written orders of a physician.

Any telephone orders from a physician shall be written and signed on the record by the person in charge, and counter-signed by the physician at the time of his next visit.

Immediate investigation of the cause of accidents shall be instituted by the home operator and any corrective measures indicated shall be adopted.

All medicines, including individual prescriptions, shall be kept in a locked cabinet.

The key for this cabinet shall be carried by or accessible to only those persons authorized by the administration to handle and dispense prescriptions and medicines to individual patients.

First aid supplies for emergency care shall be maintained in a place known and readily available to all personnel responsible for the health and well being of patients or residents.

In case of sudden illness or accident, the management of the home shall immediately call a physician and notify the person or agency who placed the patient or resident in the home.

In case of death, the physician of the patient or resident and the person or agency placing the patient or resident in the home shall be notified immediately.

A signed record of this notification, the name of the person notified and the time the notification was made shall be recorded on the chart of the patient or resident.

No home shall accept for care any seriously mentally disturbed patient or resident. Any patient or resident who, after admission to a home, shows serious mental disturbance shall be removed from the home.

ARMY MEDICAL SERVICE DIPLOMATES

Army Medical Service officers are attaining in one year almost as many specialty board certifications as the Service had on its roster ten years ago when its graduate professional training program was instituted.

In 1957, 103 of the Army's physicians and surgeons successfully passed examinations of the American specialty boards.

In 1947, the Army Medical Service census of certified officers accumulated over previous years was 140 diplomates.

One of the objectives of the educational program begun in 1947 was to stimulate medical officers' interest in certification. The total number of Medical Corps diplomates in December 1957 reached 557 with a range of thirty-four specialties and combined specialties.

In Memoriam

ABRAHAM KOVEN, M.D., sixty-three, a Detroit physician, died March 16, 1958, at University Hospital in Ann Arbor.

A native of New York City, Doctor Koven set up practice in Detroit after graduation from Windsor Collegiate Institute and the Detroit College of Medicine.

He was on the staff of Detroit Memorial Hospital, a member of the Wayne Couny Medical Society, the American Academy of General Practice, American Medical Association, Perfection Lodge 486 F. and A.M., Julius Rosenwald Post No. 128, American Legion and the Alumni Association of Wayne State University.

He also served on the Department of Health for thirty-four years.

CHARLES E. STEVENS, M.D., seventy-five, Ironwood physician, died March 4, 1958, in Ishpeming, Michigan, after almost half a century as practicing physician on the range.

Born in New York and reared in Iowa, Doctor Stevens graduated from Bloomfield, Iowa, Normal School and later from the University of Illinois Medical School, obtaining his M.D. degree in 1910. He interned at the Illinois State Hospital, coming to Ironwood in 1911 to begin practice as a member of the Oliver Iron Mining Company clinic.

He practiced in Bessemer, Michigan, where he was associated with the late Dr. W. J. Pinkerton. Then, in 1942, he moved back to Ironwood and became associated with the late Dr. A. J. O'Brien.

Doctor Stevens was a senior member of the Grand View Hospital. He was a member of Gogebic County Medical Society and served as its president for several terms. In April, 1956, the Society paid tribute to him in recognition of his services in the field of medicine.

He was a member of the American Medical Association, the Railroad Industrial Surgeons Association; the Bessemer Elks lodge; the Bessemer Lions Club and Business and Professional Men's Club; the Ironwood Kiwanis Club and several lodges of the Masonic Order including the Bessemer Masonic lodge, the Minerva Chapter of Royal Arch Masons, the Gogebic Commandery, the Francis M. Moore Consistory of Marquette and the Ahmed Temple of the Shrine of Marquette.

ROGER V. WALKER, JR., M.D., thirty-two, Detroit physician, died March 19, 1958. Doctor Walker was an instructor in surgery at Wayne State University College of Medicine and member of a family prominent in Detroit medical circles since 1892. He was the son of Dr. Roger Venning Walker, one of Detroit's best known surgeons who formerly was president of the Detroit Board of Health.

His grandfather, Dr. Frank B. Walker, was a Detroit surgeon from 1892 to 1927, and his brother, Frank B., also is an M.D.

A native of Detroit, Doctor Walker was graduated from the University of Michigan in 1947 and received his medical degree from Wayne State in 1951. He served his internship in general surgery at Wayne County General Hospital and was on the surgical staff of Detroit Memorial and Detroit Receiving Hospitals from 1951 to 1956, when he became an instructor at Wayne State University.

He was a member of Zeta Psi and Nu Sigma Nu fraternities, the Detroit Surgical Society, the Detroit Academy of Surgery, the Wayne County Medical Society and the Detroit Boat Club.

Reported figures on the reliability of the vaginal smears vary from 50 per cent to 97 per cent plus in cancer detection, and the experience of the cytologist is an important factor in the reliability of the smear reports.

* * *

Radical treatment of pelvic cancer must be based on accurate and official diagnosis, not alone on a cell smear report.

* * *

The combination of the cytologic technique with palpation, adequate visualization, and biopsy confirmation will result in definite progress in the early detection of cervical cancer.

in HAY FEVER

Family Physicians use

specific desensitization for *lasting immunity

. . . easily, pleasantly and economically

SPECIFIC DESENSITIZATION . . .

is easily accomplished, quickly and accurately by any physician. Simply scratch test each patient by using activated Barry allergens to determine what offends the patient. Then send a list of these offenders with their reactions to Barry for the preparation of a specific desensitization formula which promotes *lasting active immunity*. For scratch testing your patient, use the Barry Pollen-Pack containing 21 tests of Tree, Grass and Weed pollens including Fungi and House Dust, all botanically correct for your locality. Safe, simple, time-proven technique complete with directions for your nurse.

LASTING ACTIVE IMMUNITY . . .

is obtained by desensitizing patients for the specific irritants to which your patient reacted by the scratch test. Each desensitization formula is individually prepared for each patient according to his own needs based upon the list of irritants that you supply and the degree of reaction of each. Specific desensitization immediately *promotes active immunity* lasting longer than any other known medication. Each specific treatment is prepared in a three vial serial dilution set (20 doses) and includes a personalized treatment schedule indicating the correct interval to use between injections. For patients that have already been skin tested by any means, send their list of offenders to the Allergy Division. Prompt 7-10 day service for all Rx's.

*write for free literature

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with each Rx Specific Desensitization Set prepared according to your patient's own skin test reactions.

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MICHIGAN AUTHORS

Delmar F. Weaver, M.D., Detroit, is the author of an article entitled "Free Skin Grafts and Pedicle Flaps in the Repair of Nasal Defects," presented at the sixty-second annual session of the American Academy of Ophthalmology and Otolaryngology, October 13-18, 1957, Chicago, and published in *Transactions of American Academy of Ophthalmology and Otolaryngology*, January-February, 1958.

C. J. Tupper, M.D., and **M. B. Beckett, M.D.**, Ann Arbor, are the authors of an article entitled "Faculty Health Appraisal, University of Michigan," published in the *University of Michigan Medical Bulletin*, February, 1958.

John M. Weller, M.D., Ernest W. Reynolds, Jr., M.D., and **Richard D. Judge, M.D.**, Ann Arbor, are the authors of an article entitled "Clinical Evaluation of the Diuretic Drug Chlorothiazide," published in the *University of Michigan Medical Bulletin*, February, 1958.

Harry Vander Kamp, M.S., M.D., Battle Creek, is the author of an article entitled "Schizophrenia—A Problem Also for the Internist," published in the *Wisconsin Medical Journal*, February, 1958.

Leopold Liss, M.D., Ann Arbor, and **Francisco Gomez, M.D., Detroit,** are the authors of an article entitled "The Nature of Senile Changes of the Human Olfactory Bulb and Tract," published in AMA *Archives of Otolaryngology*, February, 1958.

E. S. Gurdjian, M.D., F.A.C.S., and **J. E. Webster, M.D., F.A.C.S.**, Detroit, are the authors of an article entitled "Thrombo-Endarterectomy of the Carotid Bifurcation and the Internal Carotid Artery," published in *Surgery, Gynecology and Obstetrics*, April, 1958.

William J. Butler, M.D., Tucson, Arizona, formerly of Grand Rapids, is the author of an article entitled, "Treatment of Wilms' Tumor: Report of Three Consecutive Ten Year Cures," published in *Southern Medical Journal*, November, 1957.

Claire L. Straith, D.D.S., M.D., Richard E. Straith, M.D., and **James M. Lawson, M.D.**, Detroit, are the authors of an article entitled "Reconstruction of the Harelip Nose," read at the meeting of the American Association of Plastic Surgeons, Skytop, Pennsylvania, May 8-10, 1957, and published in *Plastic and Reconstructive Surgery*, December, 1957.

Martin J. Urist, M.D., South Haven, is the author of an article entitled "The Effect of Asymmetrical Horizontal Muscle Surgery," published in the AMA *Archives of Ophthalmology*, February, 1958.

Leonard P. Heath, M.D., Detroit, is the author of an article entitled "The Diagnosis and Treatment of Vaginal Bleeding during Pregnancy," presented at the sixty-first annual meeting of the Sioux Valley Medical Association, February, 1957, and published in the *South Dakota Medical Journal*, March, 1958.

Herbert J. Robb, M.D., Dearborn, is the author of an article entitled "Current Concepts in the Diagnosis and Treatment of Peripheral Arterial Occlusion," published in *Clinical Medicine*, March, 1958.

Frank H. Bethell, M.D., Ann Arbor, is the author of an article entitled "Purpuras and Associated Thrombotic Conditions," presented at the Symposium on Peripheral Vascular Disease co-sponsored by the Minnesota Heart Association and the Mayo Foundation, Rochester, Minnesota, September 24, 1957, and published in *Minnesota Medicine*, March, 1958.

M. H. Hendelman, M.D., F.I.C.S., Detroit, is the author of an article entitled "Torsion of Ovarian Pedicle in a Virgin," published in *The Journal of the International College of Surgeons*," February, 1958.

Paul M. Zoll, M.D., Arthur J. Linenthal, M.D., Boston, **William Gibson, M.D.**, Detroit, **Milton H. Paul, M.D.**, and **Leona R. Norman M.D.**, Boston, are the authors of an article entitled "Intravenous Drug Therapy of Stikes-Adams Disease," published in *Circulation*, March, 1958.

George Kinsley, M.D., F.A.C.S., Detroit, is the author of an article entitled "Rectal Obstruction and Large Abdominal Mass Simulating Rectal Carcinoma," published in *The American Journal of Proctology*, February, 1958.

M. K. Newman, M.D., and **Kerwin Stief, A.B.**, Detroit, are the authors of an article entitled "Electromyographic Observation as an Aid in Clinical Diagnosis," published in *Military Medicine*, March, 1958.

Arch Walls, M.D., Detroit, is the author of an article on "Fatigue," which appeared in the section of the *Detroit Free Press*, Parade, on Sunday, March 9, 1958.

* * *

L. S. Figiel, M.D., and **D. K. Rush, M.D.**, of Detroit, are authors of an original article, "Study of Colon by Use of Hi-kilo Voltage Spot-compression Technique," which appeared in JAMA of March 15, page 1269.

F. C. House, M.D., and **S. J. O'Connor, M.D.**, Ann Arbor, are authors of an original article, "Specific Management for Lumbar and Sacral Radiculitis," which appeared in JAMA of March 15, page 1285.

E. M. Knights, Jr., M.D., of Detroit, is author of "Ultramicroanalytic methods now Adaptable for Hospital Use," which appeared under "clinical notes" in JAMA of March 8, page 1175.

* * *

Dr. Charles Gardner Child III, has been appointed professor of surgery and chairman of the department

(Continued on Page 760)

(Continued from Page 758)

of surgery at the University of Michigan Medical School, effective January 1, 1959.

Doctor Child is professor of surgery and chairman of the department at Tufts University School of Medicine, Boston, Massachusetts, which position he has held since 1953. In Ann Arbor he will fill the post left vacant by the retirement of Doctor Frederick A. Coller. Doctor Child was born February 1, 1908, in New York City and obtained his M.D. degree from Cornell in 1934.

* * *

"Social Gerontology and Its Applications" will be the theme of the 1958 Annual Conference on Aging, to be held at the University of Michigan, Ann Arbor, June 23-25. The program will be a comprehensive review of both individual and societal aging with special emphasis placed on the applications of this knowledge to such problems as retirement, employment, health, housing, counciling, recreation, religion, and education. For program write Division of Gerontology, University of Michigan, 1510 Rackhum Building, Ann Arbor.

* * *

Population Growth.—During the decades ahead, the total number of consumers will increase faster than the producers, or working population. Between 1955 and 1975, for example, the total population is expected to rise by 63 million. However, the number of non-producers—those under 20 and over 64 years of age—is expected to increase by 39 million, while the number of producers—20 to 64 years of age—is expected to increase by only 24 million. Therefore, 62 per cent of the total increase in this period will be made up of the dependent age groups and a smaller proportion of the population will be of working age.

Consequently, increases in productivity must accompany the rise in population if growing needs are to be satisfied and living standards maintained. (From—Business Economic Review, 1st Nat'l Bank of Chicago, March 1958).

* * *

Tuberculosis Patient's Diet.—The prevailing attitude at the present time is that the diet of the tuberculosis patient should very nearly approximate that of the person in good health, with somewhat more emphasis on protein and vitamin content.—Seymour M. Farber, M.D., Roger H. L. Wilson, M.D., and Nancy L. Hooper, B.S., Journal Lancet, April, 1956.

* * *

Harry M. Nelson, M.D., Detroit, Chairman of the Michigan Cancer Co-ordinating Committee and Past President of the American Cancer Society, addressed the Saginaw Valley Public Health Association in Saginaw on April 24. His subject was "What's New in Cancer Control and Treatment." One hundred and twenty-five doctors of medicine, nurses, public health workers, teachers, social workers and other civic workers attended the meeting.

(Continued on Page 762)

base or the hydrochloride alone. In addition, the average levels derived from the tetracycline base or the chlortetracycline base were higher than those produced by the corresponding hydrochloride though lower than those resulting from the mixture containing the base and sodium metaphosphate. In the study with chlortetracycline[6] capsules containing a mixture of the hydrochloride and sodium metaphosphate were also included in the crossover, and the average levels produced by these capsules were the same as with the mixture of chlortetracycline base with sodium metaphosphate.

Although the enhancement of blood levels of tetracycline by phosphate, either complexed to the tetracycline or mixed with the base or the hydrochloride, thus seemed fairly well established, some doubts still remained because certain reliable observers (including many whose results have not been published) failed to confirm the findings with the materials and methods they used. Further confusion seemed to be added by a subsequent report of Welch et al.,[7] who, in repeating a crossover study with capsules of tetracycline phosphate complex and tetracycline hydrochloride with and without sodium metaphosphate, four

antibacterial activity than was observed in their absence. Oil and sorbitol did not interfere with tetracycline absorption.

Dicalcium phosphate is widely used as a filler in various capsules, including those of the tetracyclines. The authors cite a large number of other studies that implicate the presence of calcium ions as the cause of the reduced absorption of tetracyclines and show that citric acid can partially neutralize this effect. The depressing effect of food on the serum levels of tetracycline is likewise explained by the goodly amount of minerals contained in commercial laboratory diets, and they postulate that the multivalent cations may be responsible for the poorer absorption of the drug. The authors could not explain the failure of citric acid to enhance serum concentrations when administered with tetracycline base in contrast to its marked effect when given as the hydrochloride. However, they hypothesized that the ability of citric acid to enhance serum levels of tetra[illegible] to its ability to form comple[illegible] unavailable for

"...Tetracycline hydrochloride and citric acid, in an encapsulated mixture, produced higher serum concentrations and greater urinary excretions, and hence better absorption of tetracyclines, than any other preparation studied..."

[illegible] et al.[7] indicates that in their study the capsules of tetracycline hydrochloride, chlortetracycline hydrochloride and tetracycline phosphate complex all contained dicalcium phosphate as a filler, whereas the capsules containing citric acid and sodium hexametaphosphate did not contain any dicalcium phosphate. This could clearly explain the discrepancies noted in that study. Likewise, the inconsistencies in other studies may very well have been due to the [illegible] of calcium as fillers in so[illegible] thers.

[illegible], however,

Editorial.
The New England Journal of Medicine.
258:97-99, (January 9) 1958.

(Continued from Page 760)

Robert J. Lyon, Chicago, is the new advertising manager and director of the Technical Exhibition of the American Medical Association. Bob Lyon succeeds Thomas R. Gardiner who resigned April 1, after forty-nine years of service with the AMA. Mr. Lyon has been assistant to Mr. Gardiner for eleven years.

* * *

W.M.A.—"A decade of service toward uniting the doctors of the world and raising medical standards," was the description by Austin Smith, M.D., Chicago, President of the United States Committee of the World Medical Association when this ten-year-old organization met March 13 in New York City.

"A milestone in the world medical field," was the statement of the long-time secretary-treasurer of World Medical Association, Louis H. Bauer, M.D., of Hempsted, Long Island. Congratulations, W.M.A.!

* * *

"Wayne State University Shows the Way" is the title of the lead article in *The Detroiter*, weekly publication of the Detroit Board of Commerce (February 17, 1958). The article briefly sketched the remarkable achievements, in just a few years, of WSU and outlined a few of the more important plans for the next ten years, as envisioned by a special committee appointed by President Clarence Hilberry. The story commented "that the coming years have increased enrollment and greater demands upon physical facilities and faculty members require bold, new thinking . . . a break with the tradition of the past and the formulation of a new concept in educational planning."

* * *

Seward E. Miller, M.D., is Director of the newly organized Department of Industrial Health of the University of Michigan's School of Public Health. Doctor Miller was made Director of the Institute of Industrial Health and Professor of Industrial Health and Hygiene of the University of Michigan in September, 1956. He is a University of Michigan Medical School graduate of the Class of 1931.

* * *

Grants for Research in Mental Health.—Grants for $1,000,000 recently were made to the University of Michigan and Ypsilanti State Hospital by the National Institute of Mental Health. The money will be used for research in Schizophrenia and Psychopharmacology, under the supervision of Ralph Gerard, M.D., of the University of Michigan Mental Health Research Institute.

* * *

Lee Carrick, M.D., Detroit, addressed the Faculty of Medicine of Port-au-Prince, Haiti, March 8, on "Dermabrasion for Acne Scarring."

* * *

The University of California School of Medicine announces a postgraduate refresher course to be held in Hawaii and on board the *S.S. Matsonia* from August 5 to 21, 1958. Courses will take place week-day mornings, 9:00 a.m. until 12:00 noon (afternoons, evenings are

(Continued on Page 764)

(Continued from Page 762)

free). Tuition is $125.00. For information and program, write the Director of Postgraduate Division, School of Medicine, University of California, 2025 Zonal Avenue, Los Angeles 33.

* * *

The Gerontological Society will hold its eleventh annual scientific meeting at the Bellevue Stratford Hotel, Phialdelphia, November 6-7-8. For program and information on the meeting, write Warren Andrew, M.D., Bowman Gray School of Medicine, Winston-Salem, North Carolina, Chairman.

* * *

M. K. Newman, M.D., Detroit, gave a talk on February 26, 1958 before the Detroit Chapter of the National Association of Compensation Claimant Attorneys, entitled "The Medico-Legal Aspects of Electromyography."

* * *

The Academy of Medicine of Cleveland, Ohio, had as its featured speaker at their meeting on Friday, March 21, Ralph W. Gerard, M.D., Ph.D., Professor of Neurophysiology, Neuropsychiatric Institute, University of Michigan. His subject was "Schizophrenia and Psychopharmacology."

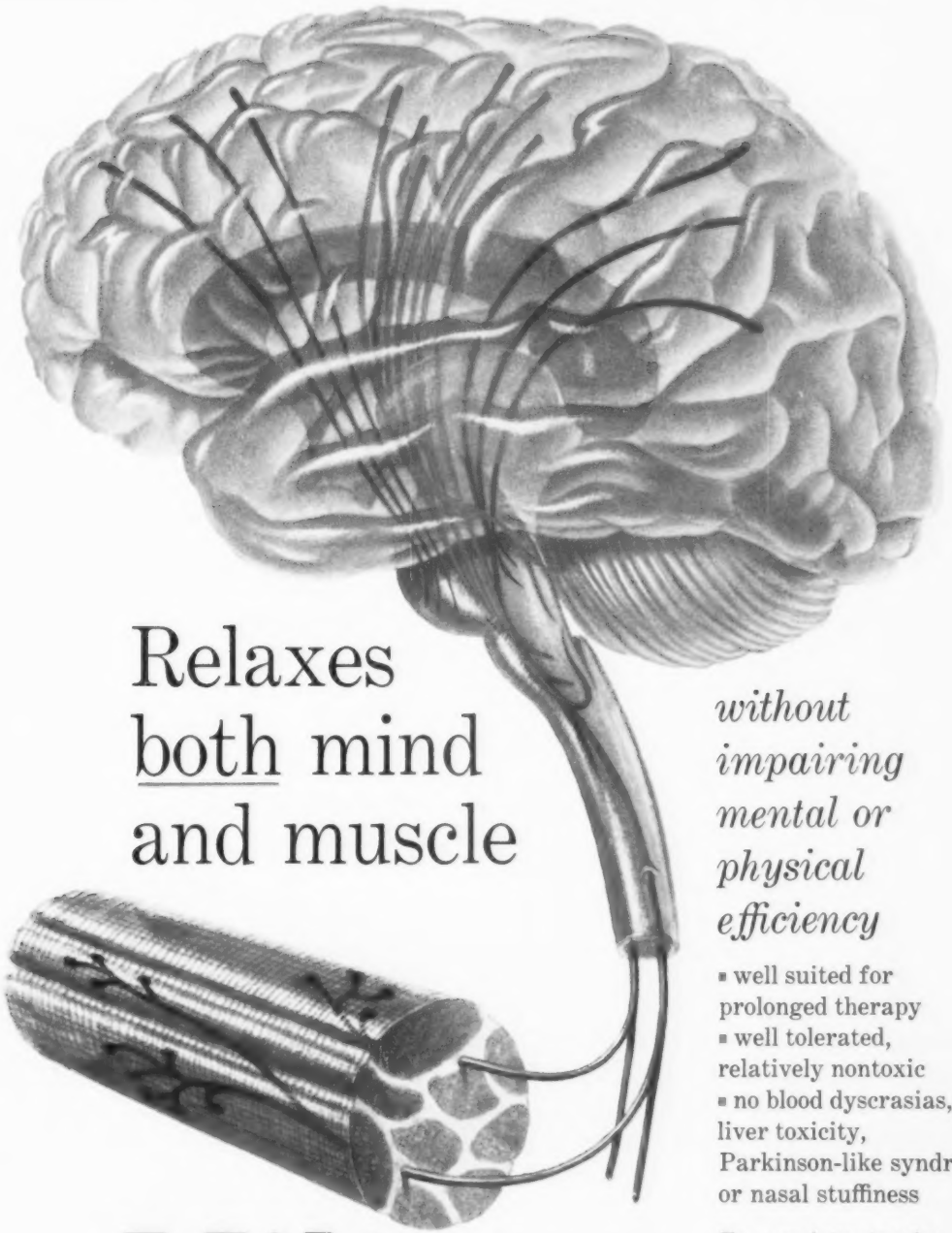
* * *

The Asia-Pacific Academy of Ophthalmology is sponsoring a good will tour of countries of the Orient following the International Congress of Ophthalmology in Brussels in September, 1958. The purpose of this tour, which is to last approximately one month, is to hold joint meetings with ophthalmologists in Pakistan, India, Thailand, the Philippines, and Hong Kong. It is expected that this good will tour will create much interest among physicians in the countries to be visited and contribute greatly to American-Asiatic medical rapprochement.

Our government has given its whole-hearted support to the plan of stimulating and facilitating a continuing exchange of information and techniques, treatments and devices for the care of the ill and the blind. The reception of a group of physicians from the West throughout Asia will certainly be most cordial and will assure the success of this enterprise. The ophthalmological and medical material in all the countries is extremely interesting and should be of great value to members of the tour.

The Asia-Pacific Academy of Ophthalmology was organized in 1957. Its principal purposes are to extend ophthalmologic knowledge and to advance the arts and sciences of ophthalmology and related sciences in Asia and in countries bordering the Pacific Ocean; . . . to stimulate research in tropical and systemic eye diseases, that are particularly prevalent in Asia and in countries bordering the Pacific Ocean; to cultivate social and fraternal relationship of physicians residing in Asia; . . . to offer postgraduate instruction in ophthalmology through the medium of lectures, round-table discussions, seminars, clinics, films and other means.

(Continued on Page 766)



Relaxes both mind and muscle

without impairing mental or physical efficiency

- well suited for prolonged therapy
- well tolerated, relatively nontoxic
- no blood dyscrasias, liver toxicity, Parkinson-like syndrome or nasal stuffiness

For anxiety, tension and muscle spasm in everyday practice.

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TRANQUILIZER WITH MUSCLE-RELAXANT ACTION

THE ORIGINAL MEPROBAMATE
DISCOVERED & INTRODUCED BY
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NEW BRUNSWICK, NEW JERSEY

Supplied:
400 mg. scored tablets,
200 mg. sugar-coated tablets.
Usual dosage:
One or two
400 mg. tablets t.i.d.

CM-6590

AN IMPORTANT ADVANCE IN MENOPAUSAL THERAPY

Because it replaces *half* control with *full* control.

Because it treats the *whole* menopausal syndrome.

Because *one* prescription manages *both* the psychic and somatic symptoms.

SUPPLIED: Bottles of 60 tablets.
Each tablet contains:

MILTOWN® (meprobamate, Wallace) ..... **400 mg.**
2-methyl-2-*n*-propyl-1,3-propanediol dicarbamate.
Conjugated Estrogens (equine) ..... **0.4 mg.**

DOSAGE: One tablet t.i.d. in 21-day courses with one week rest periods. Should be adjusted to individual requirements.
Samples and literature on request.

Two-dimensional treatment of the menopause

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MILTOWN®
A Proven Tranquilizer
+
CONJUGATED ESTROGENS (EQUINE)
A Proven Estrogen

WALLACE LABORATORIES, *New Brunswick, N. J.*
who discovered and introduced Miltown, the original meprobamate.

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A REPORT . . .

to the Doctors and Hospitals of Michigan

YOUR BLUE CROSS-BLUE SHIELD PLAN PROVIDED MORE BENEFITS FOR MORE PEOPLE . . IN 1957

Here are the facts, as of December 31, 1957:

- Michigan Blue Cross paid 547,472 hospital admissions, an increase of 2% for the year.
- Michigan Blue Shield paid for 1,307,667 medical and surgical services, an increase of 9%.
- Michigan Blue Cross enrollment stood at 3,765,609, Michigan Blue Shield enrollment at 3,750,811. Thus, 99.61% of Blue Cross members have Blue Shield, highest percentage of any Plans in the world.
- More than 18,000 Michigan business, labor, professional and farm groups now offer Blue Cross-Blue Shield coverage to their members.
- Payments to doctors and hospitals amounted to over $153-million last year alone. During their 19 years of operation, your Michigan Plans have made payments totaling $890-million for care of members.

STATEMENT OF CONDITION

Report of Condition as of the Close of Business December 31, 1957

MICHIGAN HOSPITAL SERVICE

ASSETS

Cash in Banks and Office	$ 4,926,641
Real Estate—Home Office Property	1,679,095
United States Government Securities	27,668,492
Accrued Interest	171,184
Subscription Fees—Receivable	247,278
Funds Advanced for U. S. Government Agencies	96,288
Other Assets	736,631
Total Assets	$35,525,609

LIABILITIES AND RESERVES

Reserve for Payment for Services Rendered Subscribers (Including Unreported)	$20,250,289
Reserve for Unearned Subscription Fees	7,611,636
Reserve for Contingencies	7,093,876
Other Liabilities	569,808
Total Liabilities and Reserves	$35,525,609
Total Benefits Paid Since Inception	$632,241,966

MICHIGAN MEDICAL SERVICE

ASSETS

Cash in Banks and Office	$ 2,918,242.33
Real Estate—Home Office Property	1,529,735.16
Bonds	9,252,713.47
Preferred Stocks, at Market	88,275.00
Interest, Due and Accrued	44,269.65
Subscription Fees—Receivable	117,896.31
Funds Advanced for U. S. Government Agencies	184,324.89
Other Assets	156,185.75
Total Assets	$14,291,642.56

LIABILITIES AND RESERVES

Reserve for Payments for Services Rendered Subscribers and Veterans (including unreported)	$ 7,014,390.97
Reserve for Unearned Subscription Fees	2,958,774.88
Reserve for Contingencies	4,236,991.35
Other Liabilities	81,485.36
Total Liabilities and Reserves	$14,291,642.56
Total Benefits Paid Since Inception	$256,935,528.78

BLUE CROSS-BLUE SHIELD

Michigan Hospital Service • Michigan Medical Service

441 East Jefferson Ave., Detroit 26

(Continued from Page 764)

Physicians other than ophthalmologists and their families are also welcome to join this trip!

Those desiring to participate in the postgraduate lectures and seminars on medical subjects pertinent to ophthalmology should contact William John Holmes, M.D., Liaison Secretary, Suite 280, Alexander Young Building, Honolulu 13, Hawaii.

Inquiries regarding travel arrangements should be sent to Compass Travel Bureau, 55 W. 42nd Street, New York 36, New York.

* * *

The American Psychiatric Association has announced a $100,000 grant from the Smith Kline & French Foundation to continue the Foundation's Fellowships in Psychiatry through 1960.

These fellowships were established in 1955 with a three-year, $90,000 grant from the SKF Foundation, which is principally supported by contributions from Smith Kline & French Laboratories, Philadelphia pharmaceutical firm. The program is administered by a committee appointed by the American Psychiatric Association.

In announcing the new grant, the APA said that more than 150 physicians and medical students already have benefited from SKF Foundation Fellowship awards. The programs have ranged from a study of suicide rates to extension training programs in psychotherapy and psychosomatic medicine. Almost one-third of the original $90,000 grant was used to enable staff psychiatrists from state hospitals to take advanced training at some of the nation's leading psychiatric training centers.

Visiting lectureships and teaching fellowships were established at five mental hospitals. Thirty physicians, many of them in state mental hospital service, benefited from the two extention training programs.

More than fifty medical students have been given the financial opportunity to undertake summer programs in psychiatry, thus enriching their undergraduate psychiatric studies. Of particular interest in view of the nation's need for psychiatrists is that a number of these students have indicated that they have decided to specialize in psychiatry because of their summer activities.

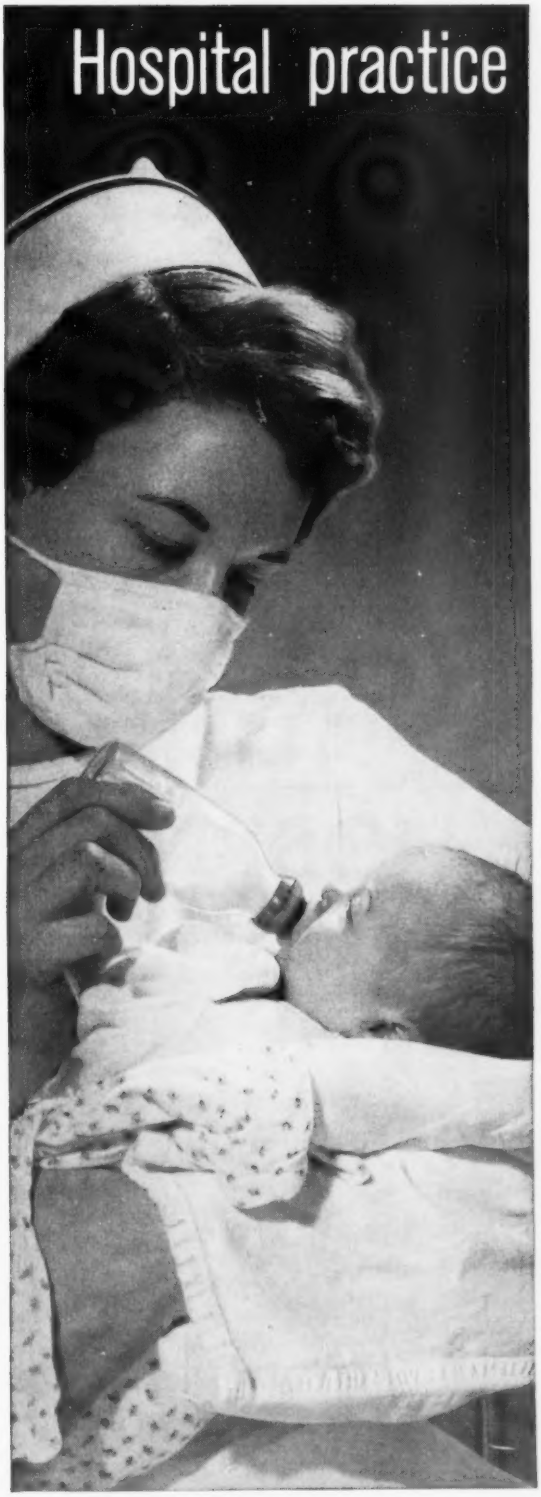
Members of the Committee are Drs. Kenneth E. Appel, Philadelphia, Chairman; Daniel Blain, Washington, D. C.; Henry Brill, Albany, New York; Jacob E. Finesinger, Baltimore; Francis J. Gerty, Chicago; Robert G. Heath, New Orleans; David A. Young, Raleigh, North Carolina, and Seymour Vestermark, Bethesda, Maryland.

* * *

American Board of Obstetrics and Gynecology applications for certification, new and reopened—Part I, and requests for re-examination—Part II, are now being accepted. All candidates are urged to make such application at the earliest possible date. Deadline date for receipt of application is September 1, 1958. No applications can be accepted after that date.

Candidates for admission to the Examinations are required to submit with their application, an unbound

(Continued on Page 768)



Hospital practice of infant feeding

Standard formulas for WELL INFANTS

Since age, appetite and digestive capacity vary, hospital practice favors an individualized formula for each infant.

The total daily feeding usually amounts to 2 ounces of milk *per pound of body weight*, plus 1 ounce of Karo Syrup with enough water to satisfy fluid requirements.

The newborn usually takes from 2 to 3 ounces of formula per feeding; the very young infant, 4 to 5 ounces—the daily quota yielding over 50 calories for each pound the infant weighs. The quantity per feeding should not exceed 8 ounces.

Newborns are fed at 3 to 4 hour intervals throughout the 24-hour period—the 2 or 3 A.M. feeding is discontinued after the neonatal period. In the third or fourth month the 10 or 12 P.M. feeding is discontinued, once the infant fails to awaken for the bottle. Standard but individualized formulas which constitute the hospital infant feeding regimen are shown here.

WHOLE MILK FORMULAS

Age Months	Cow's Milk Fluid Oz.	Water Oz.	KARO Tbsp.	Each Feeding Oz.	Feedings in 24 Hrs.	Total Calories
Birth	10	10	2	3	6	320
1	12	13	2½	4	6	390
2	15	13	3	4½	6	480
3	17	9	3	5	5	520
4	20	11	3½	6	5	610
5	23	11	4	6½	5	700
6	26	10	4	7	5	760

EVAPORATED MILK FORMULAS

Age Months	Evap. Milk Fluid Oz.	Water Oz.	KARO Tbsp.	Each Feeding Oz.	Feedings in 24 Hrs.	Total Calories
Birth	6	12	2	3	6	380
1	8	16	3	4	6	532
2	9	14	3	4½	5	576
3	10	15	3½	5	5	650
4	12	18	4	6	5	768
5	12	21	4	6½	5	768
6	13	22	4	7	5	768

ADVANTAGES OF KARO® IN INFANT FEEDING

Composition: Karo Syrup is a superior dextrin-maltose-dextrose mixture because the dextrins are nonfermentable and the maltose is rapidly transformed into dextrose which requires no digestion.

Concentration: Volume for volume Karo Syrup furnishes twice as many calories as similar milk modifiers in powdered form.

Purity: Karo Syrup is processed at sterilizing temperatures, sealed for complete hygienic protection and devoid of pathogenic organisms.

Low Cost: Karo Syrup costs 1/5 as much as expensive milk modifiers and is available at all food stores.

Free to Physicians—Book of Infant Feeding Formulas with convenient schedule pads. Write:

Medical Division
CORN PRODUCTS REFINING COMPANY
17 Battery Place, New York 4, N.Y.

(Continued from Page 766)

8½ x 11 typewritten list of all patients admitted to the hospitals where they practice, for the year preceding their application, or the year prior to their request for reopening of their application.

Current bulletins outlining present requirements may be obtained by writing to the Secretary's office, Robert L. Faulkner, M.D., 2105 Adelbert Road, Cleveland 6, Ohio.

* * *

A blood test which may prove practical for the detection of active tuberculosis has been developed at Northwestern University Medical School. The double-diffusion precipitation technique uses virulent tubercle bacilli for the antigen. The antigen substance has an agar gel base which solidifies after being pipetted into a glass tube. A second layer of agar is inserted. The tube then is filled with the blood serum to be tested for antibodies. A cloudy layer is precipitated usually within 48 or 72 hours if the serum is from a tuberculous patient. The test, which is explained in the March issue of the American Review of Tuberculosis and Pulmonary Diseases, is described as simple and reliable. It can be carried out in hospital laboratories with a minimum of equipment. However, it is only a qualitative test, providing no measurement of the amount of any of the antibodies detected.

MICHIGAN TUBERCULOSIS ASSOCIATION

Pergamon Institute has recently issued a comprehensive announcement regarding the availability of results of research and development in the U.S.S.R. and other Soviet orbit countries in the field of science, technology and medicine. This information could be of great value and utility to government departments, learned societies, technical institutes and industrial establishments, scientists, doctors, engineers, and to those interested in international scientific collaboration.

Recent reports of great scientific advance in Russia seem to demand an effort to inform ourselves. It is one of the primary functions of Pergamon Institute to fill this need by instituting large scale translation programs of complete journals, books, and individual papers in all the critical fields of science, technology and medicine.

It is also planned to hold a symposium in the summer of 1958 in Washington or London to make plans, establish extra-curricular courses, teach the Russian language and for general information. An honorary advisory council has been established including Dr. J. H. Enns and Dr. R. A. Sawyer, both of Ann Arbor.

* * *

The American Medical Golfing Association is holding its annual golf tournament in conjunction with the AMA Convention, June 23, 1958, at the beautiful Olympic Lakeside Golf and Country Club, San Francisco, California. This will be a whole day of rest and relaxation with golf, luncheon, banquet and a prize for everyone. No stone has been left unturned to assure the very best. Tee off time 8 A.M. to 2 P.M. All golfing

(Continued on Page 770)

(Continued from Page 768)

doctors are cordially invited to attend. Handicaps scratch to 30 in flights.

For information, contact James J. Leary, M.D., Secretary, 450 Sutter Street, San Francisco, California.

* * *

The American Medical Association has established a Committee on Poliomyelitis with Julian P. Price, M.D., Chairman. Dr. Price, former editor of the *South Carolina Medical Journal* and now a trustee of the AMA, is sponsoring an active campaign to have every person under forty receive polio vaccine shots. According to the United States Public Health Service, by March 1, 1958, 62,500,000 people had received one or more shots of the polio vaccine. Only 42,500,000 of these, however, had received all three injections. Sixteen million had 2 shots and are now eligible for the third, but that leaves an estimated 48,500,000 under the age of forty who have not started the Salk vaccine at all. It is urged that every effort be made by the doctors throughout the land that these people be protected. Previous to the development of the Salk vaccine, the average for the immediate five years was 38,727 paralytic cases. Last year, there were only 5,895 cases in all, of which 2,158 were paralytic. This is a marvelous improvement and should be a convincing argument. Dr. Price is urging that medical groups, medical societies, establish clinics or programs where everyone can come and get the shots. In cases where it is a hardship, a charge of $1.00 is made for the shot or it is being given gratis. Medical society endorsements of group inoculations centers in various areas of the country have demonstrated dramatically, that physician and medical society leadership gives stature to the program and insures their success. A national advertising program is under way. The Advertising Council Incorporated, New York, Washington, Chicago, Hollywood, San Francisco, with head offices in New York, has distributed material for the "Stamp out polio campaign" in newspaper advertisements. Now is the time to start the shots for protection this summer and fall. Every doctor, every newspaper is urged to lend support to this campaign and actually stamp out polio.

* * *

John C. Heffelfinger, M.D., Secretary of the Branch County Medical Society, reports that Branch County Medical Society has to its credit a Poison Control Center. Since some time in January, the Community Health Center in Coldwater has had an operation of its own Poison Control Center. This has been a cooperative effort on the part of the Branch County Medical Society, the Community Health Center and the District Health Department.

* * *

The Ninth Seminar of the World Health Organization will be held in Minneapolis, May 26 through June 4, 1958, simultaneously with the Eleventh World Health

(Continued on Page 772)

(Continued from Page 770)

Assembly. An extensive program is provided and an invitation is extended to doctors, medical students, public health and social workers, nurses and others interested. Applications and requests for information should be addressed to the Committee on General Arrangements for WFUNA-WHO Seminar, 2808 West River Road, Minneapolis 2, Minnesota.

* * *

A joint banquet of the Copper Country Medical Society and the Copper Country Bar Association was held Saturday, February 22, at Houghton, Michigan. The affair is an annual occurrence, held in observance of Washington's Birthday. Attorney Joseph Romig of Houghton, a member of the faculty of Michigan College of Mining and Technology, was the speaker of the evening.

* * *

Frederick A. Coller, M.D., of Ann Arbor, addressed the annual joint meeting of the Kent County Medical Society and its auxiliary at the Manger-Rowe Hotel, Grand Rapids, on February 12. Doctor Coller, noted as a teacher of Medical history, gave a talk on Dr. William Beaumont, accompanied by slides.

* * *

A $240,000 contract between Schering Corporation, pharmaceutical manufacturer of Bloomfield, New Jersey, and the National Institutes of Health was signed recently calling for the testing of chemicals and antibiotic culture filtrates for anti-cancer activities and for screening methodology studies.

The project is designed for screening against three specified tumors and also calls for investigations into newer methods of screening of anti-cancer compounds.

* * *

Proper artificial lighting for all phases of our daily life based on new lighting standards developed on a scientific basis was discussed at the University of Michigan's School of Public Health Short Course on Light and Vision held March 19, 20 and 21 at Ann Arbor.

Among members of the special faculty for the three-day course were Dr. H. Richard Blackwell, University of Michigan; Everett M. Strong, professor of electrical engineering, Cornell University; Dr. Franklin N. Foote, executive director of the National Society for the Prevention of Blindness; Dr. Matthew Alpern, University of Michigan; Dr. Sylvester Guth, manager of the Radiant Energy Effects Laboratory, Nela Park, Cleveland; and Dr. Robert A. Boyd, University of Michigan.

* * *

The International College of Surgeons will hold the following meetings this year:

First congress of the European Federation, Brussels, Belgium, May 15-18.

Third national congress of the Iranian Section, Teheran, May 12-15.

Fifth annual congress of the Japanese Section, Tokyo, October 17.

For information, write to the Secretariat, International College of Surgeons, 1516 Lake Shore Drive, Chicago 10.

(Continued on Page 774)

(Continued from Page 772)

"The Citizen of the Year" award was presented to Lewis E. May, M.D., Howell, on February 11 by Mayor Clifton Heller. The award is given annually by the Howell Chamber of Commerce to someone it considers worthy of this honor. Doctor May was unaware of his choice for the award until the time it was presented.

Congratulations, Doctor May!

* * *

Russell F. Staudacher, Executive Secretary of the Student American Medical Association, Chicago, and former associate public relations counsel for the Michigan State Medical Society, was recently elected a trustee of the Minnesota Mutual Life Insurance Company of Saint Paul, Minnesota.

* * *

MEDICAL TELEVISION SHOWS

Shows produced by Michigan Health Council over WJBK-TV, Detroit: March 2—Home Care—(Film—"Home Care"); March 9—Epilepsy—(Film—"Something Called Epilepsy"). Guests: Z. Stephen Bohn, M.D., Raymond D. Dennerll, Detroit; March 16—Postgraduate Medical Education. Guests: C. E. Umphrey, M.D., Brock E. Brush, M.D., Detroit; March 23—Alcoholism (Film—"David, the Profile of a Problem Drinker"); March 30—Anesthesiology as a Health Career (Film—"Anesthesiology").

* * *

M.D. LOCATIONS—THROUGH MARCH 1, 1958

Placed by Michigan Health Council: Paul G. Stein, M.D., Marquette (Prison); **Assisted by Michigan Health Council:** Rudenz Douthat, M.D., Saline.

THE DOCTOR'S LIBRARY

Acknowledgments of all books received will be made in this column, and this will be deemed by us as full compensation to those sending them. A selection will be made for review, as expedient.

ERYTHROBLASTOSIS FETALIS. New England Journal of Medicine Medical Progress Series, including Exchange Transfusion Technique. By Fred H. Allen, Jr., M.D., Clinical Associate in Pediatrics, Harvard Medical School; Associate Hematologist, The Children's Hospital; Associate Director, Blood Grouping Laboratory of Boston, and Louis K. Diamond, M.D., Associate Professor of Pediatrics, Harvard Medical School; Hematologist, The Children's Hospital; Director, Blood Grouping Laboratory of Boston, Boston. Toronto: Little, Brown and Company, 1958. Price $4.00.

This book is the answer to the doctor's prayer for a clear, concise, readable book on Erythroblastosis Fetalis.

The authors have produced a masterpiece for the aid of the doctor who has to diagnose and treat Erythroblastosis.

The section on Exchange Transfusion is an inspiration and a challenge to those who have to do this work.

ROBERT S. SIMPSON, M.D.

ULCERATIVE COLITIS. By Harry E. Bacon, B.S., M.D., Sc.D., L.L.D., F.A.C.S., F.A.P.S., Professor and Head of Department of Proctology, Temple University Medical Center, Philadelphia, Pa.; President, American Board of Proctology; Diplomate, American Board of Surgery and American Board of Proctology; Honorary Fellow; Royal Society of Medicine, Philippine College of Surgeons, International College of Surgeons, Brazilian College of Surgeons, Japanese College of Surgeons. Foreword by Alton Ochsner, B.A., M.D., Sc.D., F.A.C.S., F.A.P.S. (Hon.) Professor of Surgery, Tulane University School of Medicine; Director of Surgery, Ochsner Clinic and Ochsner Foundation Hospital, New Orleans, La.; Founder Member, American Board of Surgery; Past President, American College of Surgeons and American Cancer Society. Contributions by Paul T. Carroll, B.S., M.D., former Resident in Proctology, Temple University Medical Center, Philadelphia, Pa. Chapter on Anesthesia by Leroy W. Krumperman, M.D., Professor and Head of Department of Anesthesiology, Temple University Medical Center, Philadelphia, Pa.; Diplomate, American Board of Anesthesiology. 184 illustrations. Philadelphia and Montreal: J. B. Lippincott Company, 1958. Price, $15.00.

This book is an excellent and thorough presentation on the subject of ulcerative colitis. The author discusses all phases of the disease, from the etiology through the surgical treatment. Dr. Bacon emphasizes that approximately 60 per cent of the patients can be fairly well controlled by medical care, if they are carefully followed. Because of this, he spends considerable effort in presenting the non-surgical care and treatment of these patients. The surgical treatment, pre-operatively, and post-operatively, is also given complete consideration, and the complications are thoroughly discussed.

Dr. Alton Ochsner, to whom the book is dedicated, evaluates the book very nicely in the last chapter of the Foreword, written by himself:

"Dr. Bacon's contribution on chronic ulcerative colitis is the most complete consideration of the subject that has ever been prepared. It is so well done and so authoritative that physicians who might come in contact with the disease cannot afford to be without the book. The pathologist, even the pediatrician (because the disease does occur, although infrequently, in the patients under fifteen years of age) and the surgeon need this monograph in their libraries. There is no other place where so much factual information and critical evaluation of chronic ulcerative colitis can be obtained so readily and easily."

EDWARD M. CHANDLER, M.D.

NEW AND NONOFFICIAL DRUGS. Containing Descriptions of Therapeutic, Prophylactic and Diagnostic Agents Evaluated by The Council on Drugs (formerly The Council on Pharmacy and Chemistry) of the American Medical Association, 1958. An annual publication issued under the direction and supervision of the Council. Philadelphia and Montreal: J. B. Lippincott Company, 1958. Price $3.35.

This very useful book carries the Council's new name, Council on Drugs, and the revised title, New and Nonofficial Drugs.

BOOKS RECEIVED

DISEASES OF THE HEART AND CIRCULATION. By Paul Wood, O.B.E., M.D. (Melbourne), F.R.C.P. (London) Director, Institute of Cardiology, London. Physician, National Heart Hospital, Physician in charge of the Cardiac Department, Brompton, Hospital. Second, Revised and Enlarged Edition. Philadelphia: J. B. Lippincott Company, 1958. Price, $15.00.

PRACTICAL DIAGNOSIS AND TREATMENT OF LIVER DISEASE. By Carroll Moton Leevy, M.D., Director of Clinical Investigation, Director of the Outpatient Department, and Attending Physician, Jersey City Medical Center, Jersey City, N. J.; Consultant in Medicine, U. S. Naval Hospital, St. Albans, N. Y. Foreword by Franklin M. Hangar, M.D., Professor in Medicine, College of Physicians and Surgeons, Columbia University, New York, N.Y. Illustrations by Felix Traugott. With 84 illustrations, including 23 in full color. New York: Hoeber-Harper, 1958. Price, $8.50.

CONNECTIVE TISSUE IN HEALTH AND DISEASE. Edited by G. Asboe-Hansen, M.D., Connective Tissue Research Laboratory, University Institute of Medical Anatomy, Copenhagen, Ejnar Munksgaard. New York: Philosophical Library, 1958. Price, $15.00.

HEART BEATS

(Continued from Page 646)

FINANCE COMMITTEE

Mr. Frank N. Isbey, *Chairman*, Detroit
Mr. J. William Hagerty, Detroit
M. S. Chambers, M.D., Flint
Mr. George A. Jacoby, Detroit
Mr. Read Jenkins, Detroit
Donald S. Smith, M.D., Pontiac
Mr. Alfred T. Wilson, Detroit

The elections culminated the "Heart Day" activities at the Michigan Clinical Institute. Among the out-of-state speakers were: Edgar V. Allen, M.D., Rochester, Minnesota, nationally known cardiologist and Senior Consultant in Medicine at Mayo Clinic, and Charles H. Rammelkamp, M.D., Cleveland, Ohio, Professor of Medicine at Western Reserve University.

The Michigan Heart Association, a member of the Michigan United Fund, reported that it has appropriated almost $300,000.00 this year to forty-two cardiovascular research projects in Michigan. This brings the total appropriated to underwrite research by the Association since it was organized in 1949 to more than $1,000,000.00.

Classified Advertising

$2.50 per insertion of fifty words or less, with an additional five cents per word in excess of fifty.

FOR SALE: Well established allergy practice in a Michigan city, population 170,000. Annual gross income $50,000. Physician retiring because of ill health. Write: Box 5, 606 Townsend, Lansing 15, Michigan.

SENIOR STAFF PHYSICIAN ($11,129-$13,050 annually): Vacancy at a tuberculosis sanatorium located in Northern Michigan. One year of experience in the practice of medicine and surgery required. Many fringe benefits add to the attractiveness of the position. Write: Michigan Civil Service Commission, Lansing 13, Michigan.

FOR SALE: Well-established practice and ten-bed hospital in community of 20,000. Two-story building with living quarters in rear. Equipped with operating room, x-ray, Metropolitan delivery table and complete line of drugs. New boiler and stoker installed two years ago. Relocating due to ill health. Contact: Box 9, 606 Townsend Street, Lansing, Michigan.

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DETROIT MEDICAL GROUP of fourteen men has openings for positions in Internal Medicine, Obstetrics-Gynecology, and General Practice. Excellent opportunities for professional growth and development. Write: Box 8, 606 Townsend Street, Lansing, Michigan.

WANTED: Young or middle aged physician or recent graduated intern. Forty-hour work week, starting immediately or commitment for future date. For an exclusive NW Detroit practice, $12,000 a year guarantee plus per cent of net and chance for part of practice with no investment if satisfied. Write: Director, 19354 James Couzens, Detroit 35, Michigan.

BUSY, MATURE, Michigan General Practitioner desires associate or partner so he may curtail work. Midwest on big lake. Excellent opportunity for generalist or perhaps specialty. Accredited hospital, excellent schools, churches. Will enlarge well-equipped office. In very pretty, small city. Good fishing, hunting and boating. Write: Box 7, 606 Townsend Street, Lansing, Michigan.

FOR RENT: Medical suite now vacant in Lansing's Colonial Village Medical Building. Five rooms and laboratory on ground floor. Heat and air conditioning furnished. Contact: Harold V. Hodge, 4591 Nakoma Drive, Okemos, Michigan. Telephone: EDgewood 2-6280.

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WANTED—LOCUM TENENS: Two weeks. Michigan license. Now in surgical residency. Contact: B. F. Shockley, M.D., 2564 North 66th Street, Wauwatosa 13, Wisconsin.

Index to Advertisers

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The nutritional statements made in this advertisement have been reviewed by the Council on Foods and Nutrition of the American Medical Association and found consistent with current authoritative medical opinion.

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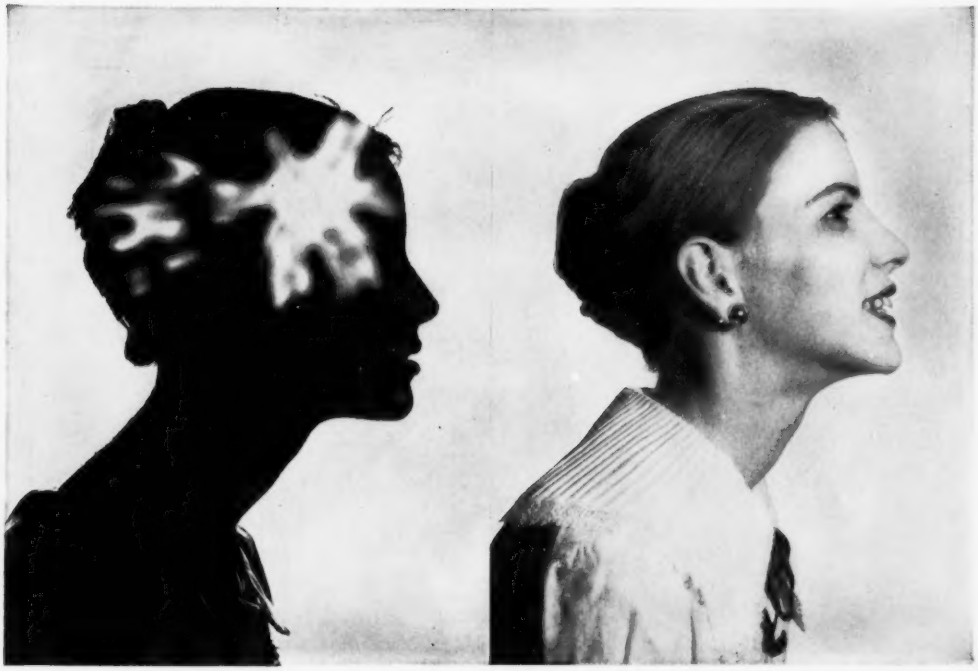

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